Impact of depression and antidepressant treatment in daily life : an experience sampling approach

Citation for published version (APA):

Barge-Schaapveld, D. Q. C. M. (2001). *Impact of depression and antidepressant treatment in daily life : an experience sampling approach*. [Doctoral Thesis, Maastricht University]. Datawyse / Universitaire Pers Maastricht. <https://doi.org/10.26481/dis.20011221db>

Document status and date:

Published: 01/01/2001

DOI:

[10.26481/dis.20011221db](https://doi.org/10.26481/dis.20011221db)

Document Version:

Publisher's PDF, also known as Version of record

Please check the document version of this publication:

- A submitted manuscript is the version of the article upon submission and before peer-review. There can be important differences between the submitted version and the official published version of record. People interested in the research are advised to contact the author for the final version of the publication, or visit the DOI to the publisher's website.
- The final author version and the galley proof are versions of the publication after peer review.
- The final published version features the final layout of the paper including the volume, issue and page numbers.

[Link to publication](#)

General rights

Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the public portal.

If the publication is distributed under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license above, please follow below link for the End User Agreement:

www.umlib.nl/taverne-license

Take down policy

If you believe that this document breaches copyright please contact us at:

repository@maastrichtuniversity.nl

providing details and we will investigate your claim.

Download date: 26 Apr. 2023

IMPACT OF DEPRESSION AND
ANTIDEPRESSANT TREATMENT IN DAILY LIFE
AN EXPERIENCE SAMPLING APPROACH

Cover illustration: Agnès Charlemagne.
Edited and printed in the Netherlands by Datawyse, Maastricht.

ISBN 90 5278 331 4

© Copyright 2001 Daniela Barge-Schaapveld. All rights reserved.
No part of this publication may be reproduced in any form by any
means without written permission of the author.

IMPACT OF DEPRESSION AND
ANTIDEPRESSANT TREATMENT IN DAILY LIFE
AN EXPERIENCE SAMPLING APPROACH

PROEFSCHRIFT

ter verkrijging van de graad van doctor
aan de Universiteit Maastricht,
op gezag van de Rector Magnificus,
Prof.dr. A.C. Nieuwenhuijzen Kruseman
volgens het besluit van het College van Decanen,
in het openbaar te verdedigen
op vrijdag 21 december 2001 om 14.00 uur

door

Daniela Quirina Carola Maria Barge-Schaapveld

Promotor:

Prof.dr. M.W. deVries

Co-promotor:

Dr. N.A. Nicolson

Beoordelingscommissie:

Prof.dr. M. Maes (voorzitter)

Prof.dr. C.M.H. Hosman

Prof.dr. H. Katschnig (University of Vienna, Austria)

Prof.dr. J.A. Knottnerus

Prof.dr. H.F. Kraan (Universiteit Twente)

*Queer little twists and quirks go into
the making of an individual.
To suppress them all and follow clock and calendar and
creed until the individual is lost in the neutral gray of the
host is to be less than true to our inheritance...
Life, that gorgeous quality of life, is not accomplished by
following another man's rules.
It is true we have the same hungers and thirsts, but they are
for different things and in different ways and in different
seasons...
Lay down your own day, follow it to its noon, your own
noon, or you would sit in an outer hall listening to the
chimes but never reaching high enough to strike your own.*

*Essay by Angelo Patri,
found in a scrapbook,
kept by Virginia,
mother of John Nash,
'A beautiful mind', Sylvia Nasar, 1998*

TABLE OF CONTENTS

PART I:	INTRODUCTION	9
	Based in part on an earlier publication by Barge-Schaapveld D.Q.C.M., Nicolson N.A., Delespaul P.A.E.G., deVries M.W., 1997. Assessing daily quality of life with the Experience Sampling Method. In: Katschnig H., Freeman H., Sartorius N., Quality of Life in Mental Disorders, John Wiley & Sons, Chichester, UK.	
CHAPTER 1	Depression and the Quality of Life (QoL)	9
CHAPTER 2	Use of the Experience Sampling Method (ESM) to assess daily QoL in clinical research	27
PART II:	PRELIMINARY STUDY (STUDY 1)	41
CHAPTER 3	Changes in daily life experience associated with clinical improvement in depression Journal of Affective Disorders, 1995, 34, 139-154	41
PART III:	MAIN STUDY (STUDY 2)	63
CHAPTER 4	Using ESM to investigate QoL in clinical trials of antidepressants: A methodological overview	63
CHAPTER 5	QoL in depression: Daily life determinants and variability Psychiatry Research, 1999, 88, 173-189	87
CHAPTER 6	Effects of antidepressant treatment on the Quality of Daily Life: An experience sampling study Journal of Clinical Psychiatry, under review	111

CHAPTER 7	The everyday experience of two depressed patients: A responder and a non-responder to treatment	131
PART IV:	DISCUSSION	141
CHAPTER 8	The impact of depression and antidepressant treatment in daily life: Conclusions and general discussion	141
APPENDICES		153
APPENDIX 1	Study 1 ESM self-report (Dutch and English)	153
APPENDIX 2	Study 2 ESM self-report (Dutch and English)	159
SUMMARY		165
SAMENVATTING		167
ACKNOWLEDGMENTS		170
CURRICULUM VITAE		173

PART I INTRODUCTION

CHAPTER 1 Depression and the Quality of Life (QoL)

Depression and the Quality of Life (QoL)¹

At some point or other in our lives, we all experience what it is to be feeling down, to lack the energy to perform the activities we should do or normally do, and to be filled with pessimistic or gloomy thoughts about matters that concern us directly. Such states can occur in one person more often or longer than in the other. Usually these states do not exceed a certain level of severity, and they pass by because one has supportive friends or family, or simply because one can cope with them. In other cases, these states are part of a pathological condition, namely major depression.

Major depressive disorder is an important diagnostic category in the two most widely used classification systems for psychiatric disorders: ICD-10 (World Health Organization, 1992) and DSM-IV (American Psychiatric Association, 1994). The DSM diagnostic criteria, used in this thesis², include depressed mood, anhedonia, significant weight loss or gain, trouble with sleeping, psychomotor agitation or retardation, fatigue, feelings of worthlessness, diminished ability to think, difficulty concentrating, and suicidal thoughts. Five or more of these symptoms are required to be present for a duration of at least two weeks for a 'case' definition, and one of the symptoms must be either depressed mood or loss of interest.

Since the 1950s, with the appearance of new drugs for the treatment of depression and the refinement of the diagnostic systems in the decades thereafter, the scientific literature has shown an ever-increasing number of articles relating to this mood disorder. Why then, yet another study on depression and its treatment? Most of the available information concerns etiologic, nosological, pharmacological, and clinical perspectives. As a result, our understanding of the phenomenology, prevalence, course, and treatment of depression has dramatically increased. But our understanding of depression and its management is far from being complete, as evidenced by the fact that depression ranks fourth in terms of global burden of disease according to the World Bank (1993). And, as depression is expected to become the second most important cause of disability world wide in 2020, additional research on depression is justifiable. In an attempt to obtain better insight into the burden of depression and its treatment on

1 This chapter is based in part on an earlier publication by Barge-Schaapveld D. Q. C. M., Nicolson N. A., Delespaul P. A. E. G., deVries. M. W., 1997. Assessing daily quality of life with the Experience Sampling Method. In: Katschnig H., Freeman H., Sartorius N. (Eds.), *Quality of Life in Mental Disorders*, John Wiley & Sons Ltd, Chichester, pp.95-107.

2 Although DSM-IV is referred to in this introductory chapter, the previous version of this diagnostic classification system, namely DSM-III-R (American Psychiatric Association, 1987), is used in other chapters of this thesis. The diagnostic criteria for major depression are identical in both versions.

the patients themselves, clinical studies have introduced new outcome measures, generally referred to as 'Quality of Life' (QoL) measures. But as will be seen, little attention has been given to the experiential aspects of depression and its treatment. That is to say, how do depressed persons experience their illness in daily life? In what kind of daily life situations do they feel most depressed? Does their inability to enjoy life in general impact on all activities they engage in? How does antidepressant treatment influence their daily life experiences? Is the improvement in mood related to specific contexts in their daily lives? How frequently during the day do treatment side effects occur, and to what extent do they impact patients' quality of life? In order to answer these types of questions, this thesis will explore daily quality of life in depressed patients and changes in daily life experiences following pharmaco-therapeutic interventions.

BURDEN OF DEPRESSION

Over the past two decades, major epidemiological studies have been conducted to determine the prevalence of depressive disorders. Although all agree that depression is a common condition, varying prevalence rates have been reported. Summarizing epidemiological studies performed since 1980, Wittchen et al. (1994) reported that the point-prevalence of major depression was about 3% (range: 1.5% – 4.9%); the 6-month to 1-year prevalence of major depression was about 6% (range: 2.6% – 9.8%) and the lifetime prevalence of major depression was about 16% (range: 4.4% – 18%).

Depression was originally described as a primarily single episode disorder. In the past decades, it has been recognized as a recurrent psychiatric disorder, in which discrete episodes of illness alternate with clearly defined 'well periods' during which patients return to their previous state of health (Keller, 1994). Expectations are that 50 to 85% of the patients experiencing a major depressive episode will experience at least one recurrence (Tweed, 1993). The chances of occurrence of a second episode are estimated at 50%, whereas the chances that a second episode will be followed by a third rise to 85% (Cassem, 1995). Angst (1988) followed patients with depression for 19 years and found that these patients spent as much as 23% of this period in depressive episodes.

Not only do the many investigations confirm that a significant number of depressed patients experience multiple episodes, but more recent results also indicate that a substantial number of depressed patients do not return to the state of well-being they had prior to their illness. Longitudinal studies confirm that major depression is often a chronic condition. Many patients have subclinical depressive syndromes between episodes; in a study of patients who were high utilizers of primary care (Katon et al., 1992), half of the subjects who had experienced one or more lifetime episodes of major depression but no current major depression still had two or more depressive symptoms. In another study, in addition to the 20% of patients who did not respond to treatment,

another 20 to 30% showed only a partial response to treatment (Fawcett, 1994). This implies that these patients continue to suffer significant psychological, physical and social impairment between episodes.

Finally, lifetime suicide rates in individuals with major depression, in treatment or not, range between 15 and 20% (Keller, 1994; Cassem, 1995; Goodwin, 1996), and the lethality of a suicide attempt increases with the severity of the depression (Malone et al., 1995). Recent epidemiological data indicate that suicide rates are often a consequence of poor diagnosis and treatment of depression and suggest that antidepressants may reduce suicide risk among depressives (Isacsson et al., 1996).

Societal burden

The magnitude of depression as a public health problem is reflected in the costs incurred by society. Although different estimates have been suggested, all represent a significant percentage of the GNP. In 1980, the total economic impact of depression in the US was estimated at more than \$US 16 billion (Stoudemire et al., 1986). In 1990, Greenberg et al. (Greenberg et al., 1993) estimated the annual cost of depression in the US at approximately \$US 44 billion. Of these totals, only a small percentage (\$US 2.1 billion and \$US 12.3 billion, respectively) was spent on direct costs of diagnosis and treatment. The remaining expenses were indirect costs associated with lost productivity in the workplace. In a study of the medical and disability costs at the First Chicago Corporation (Conti and Burton, 1994), 3% of total disability days were due to depressive disorders, and the average sick leave in employees with a diagnosis of depressive disorder was 40 work days (compared to an average work absence for somatic diagnoses of 29 days).

As a consequence of poor recognition and treatment of depression in medical settings, in addition to high levels of both psychiatric and somatic comorbidity, another important contribution to the societal burden of depression is the high level of medical utilization. In one study, the use of medical outpatient facilities was found to be substantially increased in patients with major depression (36%) compared with patients with no mental disorder (8%) (Cassem, 1995). Other studies have shown that even a minimal level of depressive symptoms was associated with increased rates of service utilization, but depressive disorders were clearly associated with the highest rates of service utilization (Johnson et al., 1992; Spitzer et al., 1994). Likewise, elderly with depressive symptoms report the need for seeing a trained counselor (Blazer and Williams, 1980) or actively seek help from health professionals (Henderson et al., 1993) more often than do their non-depressed peers.

Recognition and treatment of depression in medical settings are all the more important given that untreated depression is associated with poor medical outcomes in several somatic disorders (Goodwin, 1996). In the elderly, untreated depression or inattention

to important depressive symptoms leads to needless emotional despair, psychosocial deterioration, economic loss, physical illness and institutionalization, as well as substantial rates of suicide (Kurlowicz, 1993).

Familial burden

Manifested less in economic terms, but more in terms of impairment, disability and disruption, the consequences of depression can dramatically affect the lives of those interacting with afflicted individuals (Tweed, 1993). Looking back on his own experience as a depressed inpatient, an anonymous psychiatrist described how difficult it is for staff and relatives to deal with a depressed person, mainly due to patients' indecisiveness and ambivalence (e.g. feeling guilty when people visit or phone but feeling rejected when they do not) (Anonymous, 1990). In a study of 42 adults living with a depressed patient, respondents felt burdened in numerous ways and were particularly upset by the patient's depressive symptoms, such as lack of interest in social life, fatigue, hopelessness, and worrying (Coyne et al., 1987). In addition, 40% of these respondents were sufficiently distressed themselves to meet the criterion for needing psychological intervention. In another study (Fadden et al., 1987), spouses of 24 patients suffering from persistent depression were interviewed to find out how they were affected by the patient's illness. Results showed that the social and leisure activities of relatives suffered considerably as a consequence of the patient's illness. Almost half of the spouses interviewed (45%) felt that they had no idea what to do in a practical sense to deal with the mood disturbance of the patient and its consequences for their lives. However, the symptoms that relatives found most frequently burdensome were the 'negative' ones, such as worrying, irritability, and nagging. Because they overlapped with normal patterns of behavior, these symptoms were frequently not seen by the relative as arising from the patient's depression. Maybe as a result of this lack of insight, family members may become irritated and direct hostile criticism at their depressed relatives, thereby also increasing marital problems (Dew and Bromet, 1991).

Personal burden

The personal burden is best described by the experience of feeling impaired, incompetent, and unable to handle stress or even the demands of everyday life, as expressed by the Swiss physician and natural scientist Albrecht von Haller (1708-1777), who is believed to have suffered from depressive episodes: *'I have felt my heart succumb to its work, ready to surrender. ... My spirit which does not lack resilience, starts to succumb; the pleasure in my work is diminishing and my resources seem exhausted.'* (van Lieburg, 1988, p.51). Becoming depressed is often seen by patients as a matter of their losing a balance in various aspects of their lives (Coyne and Calarco, 1995). Depressed individuals fre-

quently complain of poor memory and concentration. Counterintuitively, however, a direct relationship between the severity of the depression and the occurrence of cognitive dysfunction has not been established (Brown et al., 1994). In addition, depressed individuals tend to appraise unpleasant events as more aversive than do non-depressed individuals (Lewinsohn and Amenson, 1978) and to attribute these negative events more often to internal causes than do patients with generalized anxiety disorder, for instance (Riskind et al., 1989). As already mentioned, depression is by definition characterized by a negative mood and an inability to enjoy life. Although this is widely accepted, it does not seem to be a sufficient basis, however, for differentiating clinical depression from ordinary blues. According to recovered patients, being depressed is different from being sad or blue because of the profound loss of energy and the disruption in everyday functioning that one experiences (Coyne and Calarco, 1995).

Indeed, having difficulties in everyday functioning is another important aspect of the personal burden experienced by depressed patients. In general, there is evidence that a low frequency of activities constitutes an extremely important clinical aspect of depression (Lewinsohn and Libet, 1972). The overall number of daytime activities depressed individuals engage in is only 70% of normal controls (Ehlers et al., 1988). Performance of daytime activities usually only occur when patients have sufficiently improved in their mood to take an interest in the activities (Anonymous, 1990). Similarly, Blazer et al. (Blazer and Williams, 1980) found a decrease in the activities of daily living in elderly depressed individuals, even though their physical health was not substantially impaired. Specifically, depressed persons engage in fewer pleasant activities than nondepressed individuals (Lewinsohn and Amenson, 1978), and the frequency with which they engage in these activities is lower than in normal controls (Szuba et al., 1992).

Social relationships in general and relationships with their families in particular become increasingly important as the social context of depressed individuals narrows. Perceptions of inadequate support are associated with both the onset and continuation of depressive symptoms (Henderson and Moran, 1983), and high levels of spouses' expressed emotion are predictive of relapses (Hooley et al., 1986). In addition, feelings of loneliness or the ending of an intimate relationship emerge regularly as precipitating factors for suicide attempts (O'Donnell et al., 1996). Although not unique to depression, social support fulfils an essential role in depressed patients. They need to be understood by and useful to the members of their social network, they need to feel that significant others are available to talk to about problems, or in any case can be counted upon (George et al., 1989). Statements elicited in two focus groups of previously depressed persons showed that feelings of guilt toward one's family also play an important role (Coyne and Calarco, 1995). The authors found that even recovered depressed patients experience secondary guilt about having been depressed, they feel the need to conceal

symptoms and impairment from others in order to avoid criticism and rejection, they sense that they are a burden on others, and they feel stigmatized.

Treatment issues

Nowadays, different alternatives are available for treating depressed patients, whereby a distinction is usually made between psychotherapy and pharmacotherapy, even though a combination of both is also believed to be effective for major depression (de Jonghe et al., 2001). The various types of psychotherapy (e.g., cognitive-behavioral, interpersonal, psychoanalytical) will not be described here, as they are not the focus of the current research. The available antidepressants can be categorized into different classes, of which the two best known - and also used in the present research - are: (1) *tricyclic antidepressants (TCAs)*, with for example, *imipramine*¹ and *amitriptyline*², and (2) *selective serotonin reuptake inhibitors (SSRIs)*, with for example, *fluoxetine*³, *paroxetine*⁴, and *fluvoxamine*⁵. In different meta-analytical reviews the two classes of drugs have not been shown to differ in efficacy (Kasper et al., 1992; Song et al., 1993). TCAs and SSRIs do differ in side effects profile as a consequence of their pharmacological actions. TCAs are known for their anticholinergic effects, which include dry mouth, constipation, and blurred vision, as well as autonomic effects, such as orthostatic hypotension, sweating, and palpitations. SSRIs are known for their gastro-intestinal side effects, such as nausea and vomiting, and sexual dysfunction. Drugs in both classes have been extensively used over the years. At the outset of this research, TCAs were still the 'first-line' treatment in many countries. Since then, most countries have turned to SSRIs as a first treatment option in view of a more favorable side effects profile. In light of still newer antidepressants (e.g. *reboxetine*⁶), suggestions have been made to revise the classification of antidepressants on the basis of a transmitter mechanism, for example (Healy, 1998).

Several studies conducted in the late 1980s (Regier et al., 1988; Klerman, 1989; Ormel et al., 1991) reported that among depressed patients who attend a general practitioner, some 50% of cases go unrecognised. In addition, two-thirds of people identified in community surveys as suffering from major depression are not receiving adequate treatments (Keller et al., 1982; Regier et al., 1988; Katon et al., 1992). Only 11% of patients evaluated as needing an antidepressant receive adequate dosage and duration of therapy (Katon et al., 1992). And when given treatment, 20 to 60% of primary care patients

1 Tofranil®

2 Tryptizol®

3 Prozac®

4 Seroxat®

5 Fevarin®

6 Edronax®

stop taking antidepressant medication because of unpleasant side effects, early recovery or, paradoxically, a worsening of depressive symptoms (Johnson, 1973; Thomson et al., 1982). The number of safe and effective medication treatments for depression has increased significantly over the past 10 years. In spite of these benefits, and in spite of the extensive and successful efforts that have been made to inform the general population about the diagnosis and treatment of depression (for instance, the Defeat Depression Campaign organized by the Royal Colleges of Psychiatrists and General Practitioners in the UK from 1992 to 1996, see Paykel et al., 1998), many patients still do not comply with treatment recommendations (Roose, 1999; Delgado, 2000). Currently, 'the treatment effect size of many antidepressants is modest, the burden of side effects they produce has never been established, and data on the quality of life during treatment is absent' (Healy, 1999).

As outlined above, not only is major depression a common illness in terms of prevalence rates but it is also a chronic illness, in the sense that individuals who are depressed will often remain so, at least intermittently, for the rest of their lives, if not committing suicide at an earlier stage. The impact of this illness is therefore immense. The burden of depression on society as a whole, but also on the families involved and the patients themselves, is huge in both economic and social terms. Still recognition of depression is far from adequate. Several treatments are available, but none is without side effects. In addition, many patients still do not comply with treatment recommendations. Therefore, our understanding of how patients experience their illness and treatment has room for much improvement. The development of QoL as an outcome measure in clinical research has offered new opportunities to shed light on the patient's perspective.

DEVELOPMENT OF QOL AS AN OUTCOME MEASURE IN DEPRESSION TRIALS

Over the second half of the twentieth century, evolving medical, governmental and industrial perspectives on health care have encouraged an optimization of treatment that reaches beyond standard medical outcome variables. Traditional indicators of the severity of illness have helped to clarify the disease pathophysiology and effects of therapy, but they do not provide insight into whether or not a particular treatment helps from the patient's perspective (Read et al., 1987). To meet these needs, QoL has developed as an outcome measure in clinical research.

Current methods of assessing QoL have developed out of three main research traditions: 'happiness', 'social indicators' and 'health status'. Each tradition has placed a different emphasis on affective, cognitive-appraisal, and behavioral components. In this section, the three QoL conceptualizations are briefly reviewed (for more detailed

reviews see Wilson, 1967; Diener, 1984; de Neeling, 1991), and the influences on the use of QoL in clinical research, in depression in particular, are outlined.

Different research traditions

The 'happiness' research tradition developed primarily out of the interests of psychologists and personality researchers; here, QoL is defined subjectively as 'feeling happy' (see, e.g. Gurin et al., 1960; Bradburn and Caplovitz, 1965; Costa and McCrae, 1980; Diener et al., 1991). 'Happiness' was first defined as a psychological construct in the 1950s (Jones, 1953), opening the way for research into its nature and determinants. In 1960, the first national study to assess the happiness of the population was carried out in the US (Gurin et al., 1960). Later it became clear that the concept of well-being should not be restricted to the extent of positive mood one feels. There is increasing agreement on the relevance of negative affect as a second independent dimension (Bradburn, 1969). Evidence for the independence of positive and negative affects stems from findings that both constructs correlate with different variables (Costa and McCrae, 1980; Abbey and Andrews, 1985): positive affect with internal control, performance, social support and extraversion, and negative affect with stress and neuroticism. Another current discussion focuses on the importance of distinguishing between short- and long-term components of happiness in models of subjective well-being (Kozma et al., 1990).

'Social indicators' research originated at the beginning of this century and reflects the interest of social scientists in economic and social determinants of well-being. The measurement of material well-being dates back to 1930, when King (1930) produced the first rough estimates of National Product to compare the living standards of different countries. In the following three decades, the definition of well-being using material indicators was refined (see, e.g. Kuznets, 1941). In the 1950s, the term 'quality of life' was introduced for the first time in this context (Ordway, 1953, p.52). Even more influential was the use of the term by President Johnson during the election campaign of 1964: 'These goals cannot be measured by the size of our bank balances. They can only be measured in the *quality of life* that our people lead' (Rescher, 1972). These political statements were confirmed in several studies that found little or no relationship between objective indicators and subjective appraisals in terms of satisfaction with life (e.g. Cantril, 1965; Rodgers and Converse, 1975; Andrews and Withey, 1976; Campbell, 1976). This led to a divergence into two lines of research. One group continued with the idea that objective indicators such as use of time (time-budgets) could also be used as social indicators of well-being (Robinson, 1977; Juster et al., 1981; Grønmo, 1982; Milbrath, 1982; Robinson, 1987). Others focused on subjective indicators; Cantril (1965), for example, asked subjects to evaluate their current life situation on a ladder from 1 (worst possible) to 10 (best possible). The idea was that QoL reflects the

size of the gap between an individual's actual situation and that to which (s)he aspires. In other words, perceived QoL is thought to result from a cognitive-appraisal process and reflects current life satisfaction. Whether this satisfaction should be measured globally or with respect to specific life domains is still the subject of debate (Lance et al., 1989; Headey et al., 1991; Feist et al., 1995).

'Health status' QoL research originated in the World Health Organization Charter of 1948. Health was defined as 'a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity'. Traditionally, the health status of a population was measured by the mortality rate or life expectancy. However, in the 1950s, the mortality rate reached a balance in Western countries, mainly due to a decrease in life-threatening diseases. It was therefore no longer a sensitive measure to differentiate the health status of different countries. On the other hand, due to the growing proportion of individuals with chronic diseases and the development of medical technology that diminished pain and discomfort without extending life, other sensitive outcome measures were needed. This led to the development of integrated and comprehensive health status indices in the late 1970s (e.g. the Nottingham Health Profile, Hunt and McEwen, 1980; the Sickness Impact Profile, Bergner et al., 1981; the SF-36, Ware et al., 1981). The 'health status' tradition has contributed a behavioral dimension to the concept: QoL represents the effect of an illness and its consequent therapy upon the patient's ability to function in daily life circumstances (Schipper, 1990).

Use of QoL in clinical research

According to some, the goal of medical interventions is not so much to decrease mortality and morbidity as to enhance the quality of life of those treated (Levine, 1987). In this sense, QoL has always been an essential outcome measure in clinical research. Although the introduction of QoL measures in clinical research is often attributed to the 'social indicators' research tradition (see Najman and Levine, 1981), there were some investigations into related concepts in clinical research prior to this date that are worth mentioning. For instance, following the introduction of nitrogen mustards in the palliative treatment of cancer, Karnofsky et al. (1948) published an article on the effects of this treatment on patients with lung cancer, measured in terms of 'subjective improvement' and 'performance status'. They developed an instrument for this purpose, the 'Karnofsky-index', which has often been referred to in later clinical trials. In 1963, independently of the three QoL research traditions, Katz et al. (1963) developed an index of independence in Activities of Daily Living (the ADL-index). It was presented as a measure of biological and psychosocial functioning for estimating the results of health care interventions in the elderly. In 1966, probably inspired by President Johnson's speech, the term 'Quality of Life' appeared for the first time in the medical literature in an edito-

rial of the 'Annals of Internal Medicine' (Elkinton, 1966, p.711). In the following two decades, the 'social indicators' tradition (e.g. Andrews and Withey, 1976; Campbell, 1976) played an increasingly influential role in QoL investigations in clinical research. The influences of the 'social indicators' research were both conceptual and methodological in nature. In the first place, the importance of the QoL concept became widely recognized (Najman and Levine, 1981; de Haes and van Knippenberg, 1985). And, despite the intangible nature of the concept, the idea that QoL can be operationalized and measured gained acceptance. QoL was acknowledged as essentially subjective and therefore only measurable by asking a judgement of the patients themselves. Popularity of the term increased, as evidenced by the introduction of 'quality of life' as a keyword in the Index Medicus in 1977. Since the mid-1980s the emphasis has shifted from a 'social indicators' approach to a 'health status' approach to QoL. By 1986, use of the terms QoL and health status had become interchangeable (Spitzer, 1987). The years thereafter have been characterized by the introduction of health status measures in clinical trials: first in somatic illnesses and more recently in psychiatric disorders. The main influences of the 'health status' tradition on QoL investigations in clinical research have been the emphasis on the importance of psychometric properties of instruments and the introduction of more functional-oriented measures. The 1990s have been marked by the development of disease-specific QoL instruments in clinical research. These instruments are often based on ideas derived from the 'social indicators' and 'health status' research traditions. With a few exceptions (e.g. de Haes et al., 1992), the 'happiness' research tradition appears to have had no influence in clinical research.

Patient's QoL, defined as a sense of well-being and ability to function in important life domains, is now commonly accepted as a (secondary) outcome measure in clinical trials.

QoL measures in depression trials

As recently summarized by Katschnig and Angermeyer (Katschnig and Angermeyer, 1997), using QoL measures in depression poses a specific conceptual problem. Intuitively, the concepts of QoL and depression are two different sides of a same coin. Indeed, suffering from psychic and somatic complaints seems to exclude someone from experiencing a high level of QoL (de Jong and Verhage, 1987). High negative correlations between measures of depression and anxiety with well-being found in some studies (Kammann and Flett, 1983; Abbey and Andrews, 1985) have led some researchers to go so far as to call depression and anxiety scales 'measures of ill-being' as opposed to well-being (Kammann and Flett, 1983). However, the relationship between the two concepts becomes more complex when time is taken into account. A depressed person may at times experience moments of high levels of QoL even though feeling depressed overall. Similarly, a non-depressed person may experience depressive states even though reporting high levels of QoL. Investigations into the relationships between QoL and depression

so far suggest that the two concepts may be related but are distinct, like measures of quantitative and verbal ability in intelligence tests (Headey et al., 1984).

In spite of these conceptual difficulties, a number of scales have been developed and used for the purpose of measuring QoL in depression trials. These instruments can be separated into two categories: generic and disease-specific. Generic QoL instruments are measures designed to cover a wide variety of domains that are relevant to QoL. They allow for comparisons to be made across conditions, but may not address sufficiently the areas relevant to depression. Some examples of generic scales used in depression trials are the Short-Form Survey (SF-36 or SF-20, Ware et al., 1994) and the Sickness Impact Profile (SIP, Bergner et al., 1981). The SF-36 was originally developed as a survey of general health status. All but one of the 36 items (self-reported health transition) are used to score eight modules (physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional and mental health). These eight modules are hypothesized to form two distinct higher-ordered clusters (physical and mental health). It has been included in various clinical trials of antidepressants (Heiligenstein et al., 1995; Philipp et al., 1999). The SIP has also been used in part or as a whole in antidepressant clinical trials (Sechter et al., 1999). This instrument consists of 12 modules of daily life activities, which can be clustered in a psychological module (emotional behavior, social interaction, alertness behavior and communication) and in a physical module (body care/movement, mobility and ambulation). The five remaining modules (sleep/rest, eating, home management, work and recreation/pastimes) are independent. Other type of generic instruments used in depression trials include objective indices of work performance, e.g. 'number of days lost from work' or 'absenteeism' (Beuzen et al., 1993), and VAS mood ratings for subjective feelings (Wheatley et al., 1998). Disease-specific scales are instruments that include all essential aspects of depression and, as such, are expected to detect any small, but clinically meaningful change in depressed patient's QoL. Although several depression-specific scales have been developed and published (e.g. SBQOL, Dunbar et al., 1992), only two have been commonly used in published trials. The first is the Quality of Life in Depression Scale (QLDS, Hunt and McKenna, 1992). The instrument is based on the theory that life gains its quality from the ability of the individual to satisfy his or her needs, with items derived from qualitative interviews with depressed or recently recovered patients. The QLDS has been used in several studies investigating the effects of fluoxetine on QoL (e.g., Mesters et al., 1993; Dam et al., 1998). The second is the Quality of Life and Enjoyment Questionnaire (Q-LES-Q, Endicott et al., 1993), designed to obtain sensitive measures of the degree of enjoyment and satisfaction experienced by subjects in various areas of daily functioning. It has mainly been used to assess the effects of the newer generation of antidepressants on QoL (Lydiard et al., 1997; Wheatley et al., 1998; Leinonen et al., 1999).

CONCLUSION

In summary, major depression is a common and chronic disease with a huge personal, familial, and societal burden. Since the 1950s, the advent of pharmacological drugs has provided new opportunities for depressed patients and over the years much effort has been made to increase the awareness of depression and its treatment. In spite of these advancements, the World Bank estimates depression to rank second in global burden of disease in 2020. Our understanding of the impact of depression and its treatment on patients' lives is far from complete. Many questions relating to how the illness is experienced in daily life or how antidepressants impinge on daily life aspects remain unaddressed or unanswered. Born out of different research traditions, the use of QoL as an outcome measure in clinical research has been steadily increasing in the past decades. In spite of conceptual difficulties with the use of QoL in depression, both generic and disease-specific scales have been applied in depression trials.

In light of the extent and burden of depression, we argue that current research approaches should be supplemented by ecological valid methods that go beyond the nosological and clinical perspectives to address the impact of depression and antidepressant treatment in the context of daily life as it is experienced. In the following chapter, an ecologically valid method will be presented. QoL approaches derived from the three research traditions and operationalized within more dynamic models of daily life experience will be described. Lastly, the potential issues arising as a result of integrating such a method in a clinical trial in order to assess the impact of antidepressants on daily life experiences will be addressed.

REFERENCES

- Abbey, A., Andrews, F. M., 1985. Modeling the psychological determinants of life quality. *Social Indicators Research* 16, 1-34.
- Andrews, F. M., Withey, S. B., 1976. Chapter 1: Introduction. In: Andrews, F. M., Withey, S. B. (Eds.), *Social Indicators of Well-Being*. Plenum Press, New-York, pp. 1-24.
- Angst, J., 1988. Clinical course of affective disorders. In: Helgson, T., Daly, R. J. (Eds.), *Depressive Illness: Prediction of Course and Outcome*. Springer, Berlin, pp. 1-44.
- Anonymous, 1990. View from the bottom. *Psychiatric Bulletin* 14, 452-454.
- American Psychiatric Association, 1987. *Diagnostic and Statistical Manual of Mental Disorders*, Third Edition, revised. American Psychiatric Association, Washington, DC.
- American Psychiatric Association, 1994. *Diagnostic and Statistical Manual of Mental Disorders*. Fourth Edition. American Psychiatric Association, Washington, DC.
- Bergner, M., Bobbitt, R. A., Carter, W. B., Gilson, B. S., 1981. The Sickness Impact Profile: development and final revision of a health status measure. *Med Care* 19(8), 787-805.
- Beuzen, J. N., Ravily, V. F., Souetre, E. J., Thomander, L., 1993. Impact of fluoxetine on work loss in depression. *International Clinical Psychopharmacology* 8, 319-321.
- Blazer, D., Williams, C. D., 1980. Epidemiology of dysphoria and depression in an elderly population. *Am J Psychiatry* 137(4), 439-444.
- Bradburn, N. M., 1969. *The Structure of Psychological Well-Being*. Aldine Publishing Company, Chicago.
- Bradburn, N. M., Caplovitz, D., 1965. *Reports on Happiness*. Aldine, Chicago.
- Brown, R. G., Scott, L. C., Bench, C. J., Dolan, R. J., 1994. Cognitive function in depression: its relationship to the presence and severity of intellectual decline. *Psychological Medicine* 24, 829-847.
- Campbell, A., 1976. Subjective measures of well-being. *American Psychologist* (February), 117-124.
- Cantril, H., 1965. *The Pattern of Human Concerns*. Rutgers University Press, New Brunswick, New Jersey.
- Cassem, E. H., 1995. Depressive disorders in the medically ill: an overview. *Psychosomatics* 36, S2-S10.
- Conti, D. J., Burton, W. N., 1994. The economic impact of depression in a workplace. *J. Occup. Med.* 36(9), 983-988.
- Costa, P. T., McCrae, R. R., 1980. Influence of extraversion and neuroticism on subjective well-being: happy and unhappy people. *J Pers Soc Psychol* 38(4), 668-678.
- Coyne, J., Kessler, R., Tal, M., Turnbull, J., Wortman, C., Greden, J., 1987. Living with a depressed person. *J Consult Clin Psychol* 55(347), 347-352.
- Coyne, J. C., Calarco, M. M., 1995. Effects of the experience of depression: application of focus group and survey methodologies. *Psychiatry* 58, 149-163.
- Dam, J., Ryde, L., Svejso, N., Lauge, B., Lauritsen, B., Bech, P., 1998. Morning fluoxetine plus evening mianserin versus morning fluoxetine plus evening placebo in the acute treatment of major depression. *Pharmacopsychiat* 31, 48-54.
- de Haes, J. C. J. M., de Ruiter, J. H., Tempelaar, R., Pennink, B. J. W., 1992. The distinction between affect and cognition in the quality of life of cancer patients - sensitivity and stability. *Quality of Life Research* 1, 315-322.
- de Haes, J. C. J. M., van Knippenberg, F. C. E., 1985. The quality of life of cancer patients: a review of the literature. *Soc. Sci. Med.* 20(8), 809-817.
- de Jong, R. D., Verhage, J., 1987. Quality of life and depression in entrepreneurs and managers. *J Hum Behav Learn* 4(2), 46-53.
- de Jonghe, F., Kool, S., van Aalst, G., Dekker, J., Peen, J., 2001. Combining psychotherapy and antidepressants in the treatment of depression. *J Affect Disord* 64(2-3), 217-229.

- de Neeling, J. N. D., 1991. *Quality of Life: Het Onderzoek naar Welzijnseffecten van Medische Handelingen*. Wetenschappelijke Uitgeverij Bunge, Utrecht.
- Delgado, P. L., 2000. Approaches to the enhancement of patient adherence to antidepressant medication treatment. *J Clin Psychiatry* 61(Suppl 2), 6-9.
- Dew, M. A., Bromet, E. J., 1991. Effects of depression on support in a community sample of women. In: Eckenrode, J. (Ed.), *The Social Context of Coping*. Plenum Press, New York, pp. 189-211.
- Diener, E., 1984. Subjective well-being. *Psychological Bulletin* 95(3), 542-575.
- Diener, E., Sandvik, E., Pavot, W., 1991. Chapter 7: Happiness is the frequency, not the intensity, of positive versus negative affect. In: Strack, F., Argyle, M., Schwarz, N. (Eds.), *Subjective Well-being: an Interdisciplinary Perspective*. Pergamon Press, New-York, pp. 119-139.
- Dunbar, G. C., Stoker, M. J., Hodges, T. C. P., Beaumont, G., 1992. The development of SBQOL: a unique scale for measuring quality of life. *British Journal of Medical Economics* 2, 65-74.
- Ehlers, C. L., Frank, E., Kupfer, D. J., 1988. Social zeitgebers and biological rhythms. *Archives of General Psychiatry* 45, 948-952.
- Elkinton, J. R., 1966. Medicine and the quality of life. *Annals of Internal Medicine* 64, 711-714.
- Endicott, J., Nee, J., Harrison, W., Blumenthal, R., 1993. Quality of Life Enjoyment and Satisfaction Questionnaire: a new measure. *Psychopharmacology Bulletin* 29(2), 321-326.
- Fadden, G., Bebbington, P., Kuipers, L., 1987. Caring and its burdens: a study of the spouses of depressed patients. *British Journal of Psychiatry* 151, 660-667.
- Fawcett, J., 1994. Antidepressants: partial response in chronic depression. *British Journal of Psychiatry* 165(Suppl. 26), 37-41.
- Feist, G. J., Bodner, T. E., Jacobs, J. F., Miles, M., Tan, V., 1995. Integrating top-down and bottom-up structural models of subjective well-being: a longitudinal investigation. *Journal of Personality and Social Psychology* 68(1), 138-150.
- George, L. K., Blazer, D. G., Hughes, D. C., Fowler, N., 1989. Social support and the outcome of major depression. *British Journal of Psychiatry* 154, 478-485.
- Goodwin, F., 1996. A 47-year-old man with chronic depression. *JAMA* 275(6), 479-485.
- Greenberg, P. E., Stiglin, L. E., Finkelstein, S. N., Berndt, E. R., 1993. Depression: a neglected major illness. *J Clin Psychiatry* 54(11), 419-424.
- Grønmo, S., 1982. Use of time and quality of life: dimensions of welfare related to specific activities. In: Staikov, Z. (Ed.), *It's about time*. The Institute of Sociology at the Bulgarian Academy of Science & The Bulgarian Sociological Association, Sofia, pp. 97-117.
- Gurin, G., Veroff, S., Feld, S., 1960. *Americans view their mental health*. Basic Books, New York.
- Headey, B., Holmstrom, E., Wearing, A., 1984. Well-being and ill-being: different dimensions? *Social Indicators Research* 14, 115-139.
- Headey, B., Veenhoven, R., Wearing, A., 1991. Top-down versus bottom-up theories of subjective well-being. *Social Indicators Research* 24(1), 81-100.
- Healy, D., 1998. Reboxetine, fluoxetine and social functioning as an outcome measure in antidepressant trials: implications. *Primary Care Psychiatry* 4(2), 81-89.
- Healy, D., 1999. The three faces of the antidepressants: a critical commentary on the clinical-economic context of diagnosis. *J Nerv Ment Dis* 187(3), 174-180.
- Heiligenstein, J. H., Ware, J. E., Beusterien, K. M., Roback, P. J., Andrejasich, C., Tollefson, G. D., 1995. Acute effects of fluoxetine versus placebo on functional health and well-being in late-life depression. *Int Psychogeriatrics* 7(suppl.), 125-137.
- Henderson, A. S., Jorm, A. F., Mackinnon, A., Christensen, H., Scott, L. R., Korten, A. E., Doyle, C., 1993. The prevalence of depressive disorders and the distribution of depressive symptoms in later life: a survey using Draft ICD-10 and DSM-III-R. *Psychological Medicine* 23, 719-729.
- Henderson, A. S., Moran, P. A. P., 1983. Social relationships during the onset and remission of neurotic symptoms: a prospective community study. *Brit. J. Psychiat.* 143, 467-472.

- Hooley, J. M., Orley, J., Teasdale, J. D., 1986. Levels of expressed emotion and relapse in depressed patients. *British Journal of Psychiatry* 148, 642-647.
- Hunt, S. M., McEwen, J., 1980. The development of a subjective health indicator. *Sociology of Health and Illness* 2, 231-246.
- Hunt, S. M., McKenna, S. P., 1992. The QLDs: A scale for the measurement of quality of life in depression. *Health Policy* 22, 307-319.
- Isacsson, G., Bergman, U., Rich, C. L., 1996. Epidemiological data suggest antidepressants reduce suicide risk among depressives. *Journal of Affective Disorders* 41, 1-8.
- Johnson, D. A. W., 1973. Treatment of depression in general practice. *British Medical Journal* 2, 18-20.
- Johnson, J., Weissman, M. M., Klerman, G. L., 1992. Service utilization and social morbidity associated with depressive symptoms in the community. *JAMA* 267(11), 1478-1483.
- Jones, H. M., 1953. *The Pursuit of Happiness*. Harvard University Press, Cambridge, MA.
- Juster, F. T., Courant, P. N., Dow, G. K., 1981. A theoretical framework for the measurement of well-being. *The Review of Income and Wealth* 27(1), 1-31.
- Kammann, R., Flett, R., 1983. Affectometer 2: a scale to measure current level of general happiness. *Australian Journal of Psychology* 35(2), 259-265.
- Karnofsky, D. A., Abelman, W. H., Craver, L. F., Burchenal, J. H., 1948. The use of nitrogen mustards in the palliative treatment of carcinoma. *Cancer* 1, 634-656.
- Kasper, S., Fuger, J., Moller, H. J., 1992. Comparative efficacy of antidepressants. *Drugs* 43(Suppl. 2), 11-23.
- Katon, W., Korff, v. M., Lin, E., Bush, T., Ormel, J., 1992. Adequacy and duration of antidepressant treatment in primary care. *Med Care* 30(1), 67-76.
- Katschnig, H., Angermeyer, M. C., 1997. Quality of life in depression. In: Katschnig, H., Freeman, H., Sartorius, N. (Eds.), *Quality of Life in Mental Disorders*. John Wiley & Sons Ltd, Chichester, pp. 137-147.
- Katz, S., Ford, A. B., Moskowitz, R. W., Jackson, B. A., Jaffe, M. W., 1963. Studies of illness in the aged. The index of ADL: a standardized measure of biological and psychosocial function. *JAMA* Sept 21, 914-919.
- Keller, M. B., 1994. Depression: a long-term illness. *British Journal of Psychiatry* 165(Suppl. 26), 9-15.
- Keller, M. B., Klerman, G. L., Lavori, P. W., Fawcett, J. A., Coryell, W., Endicott, J., 1982. Treatment received by depressed patients. *JAMA* 248(15), 1848-1855.
- King, W. I., 1930. *The National Income and its purchasing power*. NBER, New York.
- Klerman, G. L., 1989. Depressive disorders: further evidence for increased medical morbidity and impairment of social functioning. *Arch. Gen. Psychiatry* 46, 856-860.
- Kozma, A., Stone, S., Stones, M. J., Hannah, T. E., 1990. Long- and short-term affective states in happiness: Model, paradigm and experimental evidence. *Social Indicators Research* 22(2), 119-138.
- Kurlowicz, L. H., 1993. Social factors and depression in late life. *Archives of Psychiatric Nursing* 7(1), 30-36.
- Kuznets, S., 1941. *National income and its composition, 1919-1938*. NBR, New York.
- Lance, C. E., Lautenschlager, G. J., Sloan, C. E., Varca, P. E., 1989. A comparison between bottom-up, top-down, and bidirectional models of relationships between global and life facet satisfaction. *Journal of Personality* 57(3), 601-624.
- Leinonen, E., Skarstein, J., Behnke, K., Agren, H., Helsdingen, J. T., 1999. Efficacy and tolerability of mirtazapine versus citalopram: a double-blind, randomized study in patients with major depressive disorder. *Nordic Antidepressant Study Group. Int Clin Psychopharmacol* 14(6), 329-337.
- Levine, S., 1987. The changing terrains in medical sociology: emergent concern with quality of life. *Journal of Health and Social Behavior* 28(March), 1-6.
- Lewinsohn, P. M., Amenson, C. S., 1978. Some relations between pleasant and unpleasant mood-related events and depression. *Journal of Abnormal Psychology* 87(6), 644-654.

- Lewinsohn, P. M., Libet, J., 1972. Pleasant events, activity schedules, and depressions. *Journal of Abnormal Psychology* 79(3), 291-295.
- Lydiard, R. B., Stahl, S. M., Hertzman, M., Harrison, W. M., 1997. A double-blind, placebo-controlled study comparing the effects of sertraline versus amitriptyline in the treatment of major depression. *J Clin Psychiatry* 58(11), 484-491.
- Malone, K. M., Haas, G. L., Sweeney, J. A., Mann, J. J., 1995. Major depression and the risk of attempted suicide. *Journal of Affective Disorders* 34, 173-185.
- Mesters, P., Cosyns, P., Dejaiffe, G., Fanielle, J., Gilles, C., Godderis, J., Grégoire, J., De Leval, N., Meire, P., Mesotten, F., Reynaert, C., Rosillon, D., Seghers, S., Stellamans, G., Van Moffaert, M., 1993. Assessment of quality of life in the treatment of major depressive disorder with fluoxetine, 20 mg, in ambulatory patients aged over 60 years. *International Clinical Psychopharmacology* 8, 337-340.
- Milbrath, L. W., 1982. A conceptualization and research strategy for the study of ecological aspects of the quality of life. *Social Indicators Research* 10, 133-157.
- Najman, J. M., Levine, S., 1981. Evaluating the impact of medical care and technologies on the quality of life: a review and critique. *Soc. Sci. & Med.* 15F, 107-115.
- O'Donnell, I., Farmer, R., Catalan, J., 1996. Explaining suicide: the views of survivors of serious suicide attempts. *British Journal of Psychiatry* 168, 780-786.
- Ordway, S. H., 1953. *Resources and the american dream*. The Ronald Press Company, New York.
- Ormel, J., Koeter, M. W. J., van den Brink, W., van de Willige, G., 1991. Recognition, management, and course of anxiety and depression in general practice. *Arch Gen Psychiatry* 48, 700-706.
- Paykel, E. S., Hart, D., Priest, R. G., 1998. Changes in public attitudes to depression during the Defeat Depression Campaign. *Br J Psychiatry* 173, 519-522.
- Philipp, M., Kohnen, R., Hiller, K. O., 1999. Hypericum extract versus imipramine or placebo in patients with moderate depression: randomised multicentre study of treatment for eight weeks. *BMJ* 319(7224), 1534-1538.
- Read, J. L., Quinn, R. J., Hoefer, M. A., 1987. Measuring overall health: an evaluation of three important approaches. *J. Chron. Dis.* 40(Suppl. 1), 7S-21S.
- Regier, D. A., Hirschfeld, R. M. A., Goodwin, F. K., Burke, J. D., Lazar, J. B., Judd, L. L., 1988. The NIMH depression awareness, recognition, and treatment program: structure, aims, and scientific basis. *Am J Psychiatry* 145(11), 1351-1357.
- Rescher, N., 1972. *Welfare. The social issues in philosophical perspective*. University of Pittsburgh Press, Pittsburgh.
- Riskind, J. H., Castellon, C. S., Beck, A. T., 1989. Spontaneous causal explanations in unipolar depression and generalized anxiety: content analysis of dysfunctional-thought diaries. *Cognitive Therapy and Research* 13(2), 97-108.
- Robinson, J., 1977. *How Americans use time: a social-psychological analysis of everyday behaviour*. Praeger, New York.
- Robinson, J. P., 1987. Microbehavioral approaches to monitoring human experience. *J Nerv Ment Dis* 175, 514-518.
- Rodgers, W. L., Converse, P. E., 1975. Measures of the perceived overall quality of life. *Social Indicators Research* 2, 127-152.
- Roose, S. P., 1999. Tolerability and patient compliance. *J Clin Psychiatry* 60(Suppl 17), 14-17; discussion 46-48.
- Schipper, H., 1990. Guidelines and caveats for quality of life measurement in clinical practice and research. *Oncology Williston Park* 4(51), 51-57.
- Sechter, D., Troy, S., Paternetti, S., Boyer, P., 1999. A double-blind comparison of sertraline and fluoxetine in the treatment of major depressive episode in outpatients. *Eur Psychiatry* 14(1), 41-48.
- Song, F., Freemantle, N., Sheldon, T. A., House, A., Watson, P., Long, A., Mason, J., 1993. Selective serotonin reuptake inhibitors: meta-analysis of efficacy and acceptability. *BMJ* 306(683), 683-687.

- Spitzer, R. L., Williams, J. B. W., Kroenke, K., Linzer, M., Verloin deGruy, F., Hahn, S. R., Brody, D., Johnson, J. G., 1994. Utility of a new procedure for diagnosing mental disorders in primary care. *JAMA* 272(22), 1749-1756.
- Spitzer, W. O., 1987. State of science 1986: quality of life and functional status as target variables for research. *J Chronic Dis* 40(6), 465-471.
- Stoudemire, A., Frank, R., Hedemark, N., Kamlet, M., Blazer, D., 1986. The economic burden of depression. *General Hospital Psychiatry* 8(6), 387-394.
- Szuba, M. P., Yager, A., Guze, B. H., Allen, E. M., Baxter, L. R., 1992. Disruption of social circadian rhythms in major depression: a preliminary report. *Psychiatry Research* 42, 221-230.
- Thomson, J., Rankin, H., Ashcroft, W., Yates, C. M., McQueen, J. K., Cummings, S. W., 1982. The treatment of depression in general practice: a comparison of L-tryptophan, amitriptyline, and a combination of L-tryptophan and amitriptyline with placebo. *Psychological Medicine* 12, 741-751.
- Tweed, D. L., 1993. Depression-related impairment: estimating concurrent and lingering effects. *Psychological Medicine* 23(2), 373-386.
- van Lieburg, M. J., 1988. Famous Depressives: Ten Historical Sketches. Organon International bv., Oss, The Netherlands.
- Ware, J. E., Brook, R. H., Davies, A. R., Lohr, K. N., 1981. Choosing measures of health status for individuals in general populations. *Am. J. Public Health* 71, 620-625.
- Ware, J. E., Gandek, B., group, I. p., 1994. The SF-36 health survey: development and use in mental health research and the IQOLA project. *Int. J. Ment. Health* 23(2), 49-73.
- Wheatley, D. P., Van Moffaert, M., Timmerman, L., Kremer, C. M. E., Group, M.-F. S., 1998. Mirtazapine: efficacy and tolerability in comparison with fluoxetine in patients with moderate to severe major depressive disorder. *J Clin Psychiatry* 59(6), 306-312.
- Wilson, W., 1967. Correlates of avowed happiness. *Psychological Bulletin* 67(4), 294-306.
- Wittchen, H. U., Knauper, B., Kessler, R. C., 1994. Lifetime risk of depression. *British Journal of Psychiatry* 165(Suppl. 26), 16-22.
- World Bank, 1993. *World Development Report - Investing in Health*. Oxford University Press, Oxford.
- World Health Organization, 1992. *The ICD-10 Classification of Mental and Behavioural Disorders: Clinical Descriptions and Diagnostic Guidelines*. World Health Organization, Geneva.

PART I INTRODUCTION

CHAPTER 2

Use of the Experience Sampling Method (ESM) to assess daily QoL in clinical research

Use of the Experience Sampling Method (ESM) to assess daily QoL in clinical research¹

EXPERIENCE SAMPLING METHOD (ESM)

ESM is a time-sampling methodology designed to study subjective experience in the natural context of daily life. It provides a description of mental states across situations, time, and places. An electronic device is used to cue subjects to report their activities, thoughts and moods at semi-random time points throughout the day. The ESM self-report, the electronic device, and the sampling frequency used may vary depending on the objective of the study (Csikszentmihalyi and Larson, 1987; Delespaul, 1995).

Development and applications of ESM

In the past 20 years, ESM has been applied by different research groups in a large number of studies addressing a variety of clinical questions (for an overview, see deVries, 1992a). Originally starting in developmental psychology as a method to obtain data on daily activities and experiences of adolescents (Csikszentmihalyi et al., 1977), sampling techniques such as ESM have subsequently been used to investigate, for example, the stream of conscious thought in daily life (e.g., Klinger et al., 1980), the effect of urbanization on daily life (e.g., Hormuth, 1986), thought content (e.g., Hurlburt and Melacon, 1987), optimal experience (e.g., Massimini and Carli, 1988), stress (Nicolson, 1992; van Eck, 1996), and the experience of psychopathology in natural settings (deVries, 1987; deVries, 1992a; deVries, 1997). In Maastricht, a broad range of psychiatric and psychosomatic disorders have been studied to date, including pain (Portegijs, 1996), heroin addiction (Kaplan, 1992), anxiety (deVries et al., 1987; Dijkman-Caes, 1993), depression (Kraan et al., 1992; Wilson et al., 1992; Barge-Schaapveld et al., 1999), and schizophrenia (Delespaul and deVries, 1987; Delespaul, 1995; Myin-Germeys et al., 2000). These studies provide evidence for the utility of ESM in describing clinically significant within-day variations in experience and symptoms, in identifying contributions of context and setting to illness or well-being, in refining current diagnostic categories, and in delineating time use patterns of psychiatric and non-psychiatric groups.

¹ This chapter is based in part on an earlier publication by Barge-Schaapveld D. Q. C. M., Nicolson N. A., Delespaul P. A. E. G., deVries. M. W., 1997. Assessing daily quality of life with the Experience Sampling Method. In: Katschnig H., Freeman H., Sartorius N. (Eds.), *Quality of Life in Mental Disorders*, John Wiley & Sons Ltd, Chichester, pp.95-107.

ESM in practice

A typical ESM period consists of three parts: a briefing interview (lasting 1 hour) the day before sampling begins, a sampling period of 6 days, and a final interview, or 'debriefing' (lasting 1/2 hour).

During the briefing session, which is usually carried out by a research nurse trained in ESM, the subject is instructed about the sampling procedures and the use of the signalling device, a digital wristwatch. The subject practices completing an ESM form. Anticipated difficulties in the use of ESM in daily life (e.g., taking a shower, driving a car) and possible solutions are discussed. Subjects are allowed to turn off the signalling device in situations when the signal would be unduly disruptive (e.g., a daytime nap), but are asked in these cases to document the time period elapsed and the reason for turning off the watch. Finally, the subject is instructed to contact the research nurse at a telephone number listed in the booklet, in case of any questions or problems with either the self-report form or the watch.

During the sampling days the subject completes self-reports (see for examples, Appendices 1 & 2), collated per day in a booklet, at semi-random time points throughout the day, typically from 7:30 in the morning to 10:30 in the evening. Additional information is recorded each day immediately after waking (sleep quality, duration of sleep, delay in falling asleep, and number of awakenings) and again before going to sleep (timing of meals, timing of switching off the watch, effects of participation in the study).

At the debriefing session, the wristwatch and the booklets are returned. The research nurse reviews the booklets and discusses all responses that are missing, illegible, unclear, or inconsistent. This is done in order to limit potential coding problems of open-ended questions (e.g., where are you?). Subsequently, the subject is asked in a structured interview about the possible impact the study might have had on mood, thoughts, and activities in daily life.

ECOLOGICALLY VALID METHODS TO INVESTIGATE QOL

Rationale

Across the three research traditions that have played an important role in the operationalization of the QoL concept (see Chapter 1), a number of issues appear to be unresolved or unaddressed. The first controversy concerns the stability of QoL over time - more specifically, whether QoL reflects a top-down or a bottom-up process (Lance et al., 1989; Headey et al., 1991; Feist et al., 1995). If we are interested in changes in QoL resulting from either the natural course or the treatment of an illness,

we would like to understand, for example, how the illness impinges on daily experiences of positive emotions, rewarding situations and the satisfying use of productive and leisure time - inherently a bottom-up approach. However, while such daily experiences are made up of states that vary from moment to moment, it is clear that a QoL index should be a summary measure of experiences over some representative period of time.

A second issue concerns the reliability of the available QoL measures. In 'health status' studies, individuals are asked to evaluate how the illness and its therapy affect their lives. However, traditional retrospective assessments of objective as well as subjective QoL dimensions are prone to a number of potential biases. Prospective monitoring of behaviors in time budget research allows more accurate measures of frequencies and duration of activities than is possible with retrospective questionnaires (Juster and Stafford, 1985). For subjective QoL data (emotions), retrospective bias has been well documented, and effects of social desirability (Milbrath, 1982; Diener et al., 1991; Veenhoven, 1991) and recall errors (Lehman and Burns, 1990) have been reported.

The third issue is ecological validity (Bronfenbrenner, 1979). Beyond the reliability issues involved, the emotional states elicited during traditional assessment situations such as clinical interviews are not necessarily the same as those occurring in natural environments. Lack of ecological validity may occur as a consequence of office-based reports bias (e.g., white coat hypertension), subject manipulation (e.g., pain reports biased by desire to influence the treating physician) or failure to sample patients' typical roles, activities, and settings (e.g., symptom report influenced by whether patient is at work or at leisure) (Stone et al., 1999).

Models of daily QoL

The problems described in the previous section have stimulated a search for new models and methods for assessing daily QoL. For example, parameters of daily life experience such as the diversity of different activities or the variability of behaviors carried out from moment to moment have been related to QoL (Delespaul, 1995). According to this formulation, QoL will be higher when individuals have contact with a variety of different persons and carry out a wider variety of activities. QoL is also expected to be higher when social contacts are distributed over time, instead of being concentrated all in one day, with social isolation the rest of the week. Similarly, QoL will be low when the same activities have to be performed for extended periods of time without a break. But QoL is not an objective state. While it might be true that most people prefer variability to continuously performing the same task, the concept of QoL points to the crucial role of subjective experience. Daily QoL is not then restricted to what subjects actually do in reference to some absolute norm, but incorporates the concurrent assessment of the individual's mood state. For example, 'being alone' most of the time is only a problem if a person experiences his worst mental states in that context. Nor, obviously, does being

in social contexts improve QoL if these are experienced as negative. Knowledge of individual preferences and experiences is thus vital for understanding QoL.

'Objective happiness' was introduced by Kahneman (1999) as a bottom-up approach to the analysis of well-being, derived from a record of the quality of experience at each 'point-instant utility'. Instant utility is an attribute of experience (being pleased or distressed) at a particular moment and is defined as the strength of the disposition to continue or to interrupt the current experience. Objective happiness is therefore the average of utility over a period of time and contrasts with 'subjective happiness', which is assessed by asking respondents to state how happy they have been throughout that same period of time.

The 'Flow' model conceptualizes optimal experience as a state in which positive mood, motivation, alertness, concentration, and control are high while negative mood is low. According to the theory, this state is most likely to be attained in the context of activities that are challenging and in which the individual is skilled (Massimini and Carli, 1988; Csikszentmihalyi, 1990). The subjects of studies contributing to the development of 'Flow' theory were primarily artists, mountain climbers, and high achievers in school. One might question whether mentally ill patients pursue optimal experience by maximizing 'Flow'. Escaping stagnation, boredom, and negative feelings may represent an equally great improvement in daily QoL in many psychiatric patients (Massimini et al., 1992).

Bringing daily life in line with personal tasks as suggested by Cantor et al. (Cantor et al., 1991) may also be regarded as a daily QoL model. Indeed, individuals who find ways to work on their most important or most rewarding tasks in their day-to-day life may experience increased emotional involvement, positive affect, and satisfaction in daily life.

Finally, according to a daily QoL model formulated by Brandstätter (1994), an important determinant of well-being may be the adequacy of the fit between person and environment. Here, states of well-being are hypothesized to be dependent on the correspondence between an individual's goals, or motives, and the gratification provided by the environment in terms of specific behavior settings.

In summary, we propose that the QoL approaches derived from 'happiness', 'social indicators' and 'health status' traditions may be operationalized within more dynamic models of daily life experience. New data and models that include the frequency of and variability in doing activities one likes, a dense record of the quality of experience at each point-instant utility, the experience of well-being that comes about when challenges and skills are in optimal balance, the time spent on tasks that are relevant and rewarding for the individual, and the goodness of fit between an individual and his environment form a starting point for operationalizing and further exploring QoL in real life settings.

The objective of this research is to investigate the contribution of dynamic models of daily life experience to the field of clinical research in depression.

APPLICATION OF ESM IN CLINICAL RESEARCH

In clinical research, the randomized controlled trial (RCT) has evolved as a major research methodology for the rigorous evaluation of new medical interventions and therapies. RCT requires an appropriately selected control treatment, randomization to the treatments, and 'blinded' assessments of response (Schatzberg and Kraemer, 2000). The typical depression trial is designed simply to determine whether a drug, in comparison with a placebo control and/or a standard antidepressant, can significantly reduce the severity of, or completely resolve a depressive disorder (Katz, 1998).

Rationale

In recent years, the increasing occurrence of 'failed' clinical studies (either negative or inconclusive) in psychiatric disorders in general, and in depression in particular, has triggered major discussions at international level among industry, academia, and regulatory agencies about the adequate use of placebo, the true drug effect of antidepressants, the choice of outcome measures, and the design of RCTs in depression¹.

In spite of numerous clinical studies that are performed throughout the different phases of a drug's development process as required for the approval of a New Drug Application (NDA), it is striking how little clinicians know about a new antidepressant at the time it is first approved for general use (Thase, 1999). Effects of drugs are estimated as the difference between the drug response and the placebo response. But because the nature of the placebo response is not fully understood and may vary according to the characteristics of the depressed group selected, concerns have been raised about the 'true' antidepressant drug effect (Kirsch and Sapirstein, 1998; Antonuccio et al., 1999). Substantial placebo response is quite common in major depression, with average placebo response rates across studies in the order of 30 to 40% (Trivedi and Rush, 1994) and some individual studies reporting rates as high as 70% (Brown et al., 1988). On average, drug-placebo differences in global response in RCTs are believed to be in the order of only 18 to 20%, with one third of all published RCTs of proven anti-

¹ for example: ECNP Consensus Meeting on 'Alternatives to placebo-controlled trials in psychiatry', September 26, 1996, Amsterdam; ACNP satellite symposium on 'Multi-site clinical trials: can they be improved?', 1997, Hawaii; ECNP Consensus Meeting on 'The failure of placebo-controlled studies', September 13, 1997, Vienna; conference organized by the National Depressive and Manic-Depressive Association on 'Clinical trials in mood disorders: the use of placebo ...past, present, and future', September 14-15, 1999, Washington, DC.

depressants failing to show drug-placebo differences (Thase, 1999). In over 30 years of double-blind placebo-controlled antidepressant trials, the most widely used primary outcome measure has been the Hamilton Rating Scale for Depression (HDRS, Hamilton, 1960), even though it was never developed with that intent and despite questions raised as to whether the HDRS can accurately measure change in the severity of meaningful depressive symptoms (Gibbons et al., 1993). The main focus of pharmaceutical industries throughout the clinical development process of an NDA in depression, in all these years, was and still is on differentiating the antidepressant compound from placebo by at least 4 points on the HDRS (which is regarded to be a clinically significant difference) at the end of treatment, on the basis of an intent-to-treat analysis (an analysis that includes all drop-outs on treatment). Little or no attention has been given to obtain a deeper understanding of the treatment effects found (e.g., do treatment effects vary during the day, or according to activities?) so as to inform clinicians more adequately on the potential use of the new antidepressant. Approaches such as ESM that generate experiential information may contribute substantially to a better understanding of these treatment effects.

The model for the typical depression trial was designed in the 1960s. The first FDA guidelines for such trials were proposed in the 1970s and revised in the late 1980s and early 1990s (Thase, 1999). This model is still recommended by the Food and Drug Administration (FDA) in the US as well as the European Agency for the Evaluation of Medicinal Products (EMA) as the 'gold standard' approach to the evaluation of treatments, despite serious questions about the integrity of the double-blind procedure (Antonuccio et al., 1999) and suggestions for new paradigms (Katz, 1998; Montgomery, 1999; Thase, 1999). A fundamental concern in the design of a RCT is to ensure adequate statistical power, meaning that if a treatment difference exists that is clinically meaningful, it is detected. There are two ways of increasing the power of a test: increasing sample size or increasing effect size. In an attempt to address the issues surrounding the placebo response, the strategy over the past decades has been to increase the sample size at a cost of additional time and expense, from typically $N = 30$ per treatment arm in the early years to $N = 100$ in more recent years. However, in an attempt to shorten drug development time, the focus is shifting from increasing sample size to increasing effect size (Leon et al., 1993; Schatzberg and Kraemer, 2000), and a search for more sensitive and reliable instruments as outcome measures is ongoing (Leon et al., 1995; Faries et al., 2000). In this respect, outcome measures based on repeated measurements may turn out to be more sensitive than the conventional retrospective questionnaires used thus far. ESM provides a potential means for reducing the number of subjects required, thereby reducing treatment research burden and number of subjects exposed to placebo, without decreasing the statistical power needed to detect a true treatment difference.

Methodological and practical issues

In applying ESM to the context of clinical trials, several methodological and practical issues can be anticipated. These issues need to be addressed during the design of a clinical trial.

Research alliance. ESM demands a look into the private world and experience of the subject over a prolonged period of time. In addition, more effort and time is required from the subject than for a questionnaire or interview. In order to obtain good compliance and accurate reporting, special care must be taken in creating a research alliance and a mutual understanding about the procedures and aims of the study. Even though in clinical trials a similar alliance would be required between patient and physician to ensure treatment adherence, the alliance for an ESM study should be even stronger, as the patient is asked to disclose personal experiences.

Subject recruitment. Subject recruitment is always a critical issue in the conduct of commercial RCTs, as any delay occurring in the development of a compound represents less return on investments. ESM is a very demanding assessment method. The additional burden imposed on subjects by ESM may reduce the number of potential candidates for the study and as such may introduce a selection bias, endangering thereby the generalizability of the study findings. In addition, some potential candidates may not be able to comply with ESM. Previous ESM studies have encountered difficulties in sampling elderly subjects with dementia, individuals with severe melancholia, acutely psychotic patients, and recently treated alcoholics (deVries, 1992b; Kraan et al., 1992; Wilson et al., 1992; Litt et al., 1998). Also, little information is available on compliance of subjects who participate in more than one sampling period in a short timeframe, as would be the case in the context of RCT.

Sampling strategy. The main focus of RCT is the comparison between pre- and post-treatment depressive states. Within this framework, the sampling strategy, in terms of frequency and density, is a compromise between compliance and sampling requirements (Delespaul, 1992). Too many sampling moments may lead to low compliance with ESM, whereas too few sampling moments may jeopardize the representativeness of daily life.

Interpretation of results. Traditional primary outcome measures used in RCTs in depression are clinician ratings such as the HDRS, often assessed on a weekly basis. In the interpretation of results, it should be taken into account that any discrepancies found between clinician and ESM measures may be the result of having: (1) observer-ratings

versus self-ratings, (2) one-time measurement versus repeated measurement, (3) retrospective versus prospective ratings, and (4) clinical versus QoL measures.

Study conduct. As was seen in the previous section, the clinical research realm is one of regulations and strict guidelines. As a consequence, the conduct of RCT is laborious and highly precise. In applying ESM to such a context, the researcher adds logistical challenges to the study conduct. In a standard clinical trial, the researcher needs to educate the physician; adding ESM, the researcher needs to educate the patient on top of that!

PRESENT RESEARCH: AIMS AND STUDY QUESTIONS

As ESM had not previously been used in the context of a clinical trial¹, we conducted a pilot study (Study 1), which was a 6-week, single-blind investigation of the effects of two active treatments (fluvoxamine and amitriptyline, known to differ in side effects profile) on the daily life experiences of major depressed patients. In addition, it provided an opportunity to address issues such as compliance with ESM, ease of use, and design of the ESM form (see Appendix 1). Results of this study are presented in Chapter 3. The main study (Study 2) was set up based on the experience of the pilot study. Several changes were made in the design: (1) inclusion of a healthy control group, (2) inclusion of a placebo-treated group, (3) double-blind design, (4) addition of a sampling period in the first week of treatment to better capture the experience of side effects, and (5) longer-term follow-up. The ESM form (see Appendix 2) was also adapted, as described in Chapter 4. In Study 2, depressed patients were randomized to either imipramine or placebo, which they could receive for up to 6 weeks, with a possible prolongation to 18 weeks. In addition, healthy controls participated in at least one ESM period. Chapter 4 provides a methodological overview of the use of ESM to investigate QoL in clinical trials of antidepressants. Chapter 5 compares the daily life experiences of depressed patients prior to treatment to the group of healthy controls similar in sociodemographic characteristics. In Chapter 6 the effects of antidepressant treatment, both in terms of side effects and efficacy, on daily life experiences are investigated. Finally, in Chapter 7, two case studies are presented as an illustration of results.

¹ Since then, a non-pharmacological intervention study has been published that used ESM measures to evaluate the effect of a tape-recorded relaxation intervention on well-being, self-reported symptoms, and pulmonary function in adult asthmatics (Smyth et al., 1999). More recently, Shiffman et al. (2000a; 2000b) published two studies that used ESM to investigate the effects of pharmacological treatments on nicotine craving and withdrawal symptoms during smoking cessation. To our knowledge, these three studies are the only other applications of ESM in intervention studies that have been published to date.

The aim of the present research was to assess the impact of depression and antidepressant treatment in daily life. To this end, an ecologically valid method, such as ESM, was needed that captures subjective experiences prospectively in real-life settings. Such a method had not been applied to a clinical trial context at the outset of the current research. Therefore, the issues explored throughout these two studies and across the different chapters reflect two central goals:

I. To determine the feasibility and utility of ESM in studying the impact of depression and antidepressant treatment in daily life.

- Is ESM well accepted by patients participating in the context of a clinical drug trial? (Chapters 3 & 4)
- How stable are ESM data over time? (Chapter 4)
- Can ESM pick up changes in daily life domains following treatment that traditional measures (generic or disease-specific QoL scales) fail to pick up? (Chapter 3)
- Does ESM improve statistical power? (Chapter 4)

II. To obtain new insights into the impact of depression and antidepressant treatment (both in terms of efficacy and side effects) on daily life. More specifically:

- What is the general impact of depression on daily mood states, physical complaints, activity patterns and enjoyment of activities? (Chapter 5)
- What are the effects of concurrent daily life experiences (negative and positive affect, physical complaints and enjoyment of activities) on QoL as it is experienced from moment to moment? (Chapter 5)
- Is instability in QoL levels characteristic for depressed patients and does antidepressant treatment reduce instability? (Chapters 5 & 6)
- How is clinical improvement following antidepressant therapy reflected in aspects of depressed patients' daily life experiences? (Chapters 3 & 5)
- How does the experience of side effects in daily life impact depressed patients' QoL? (Chapter 6)
- Does antidepressant treatment effectively improve QoL in daily life to what can be regarded as 'normal' levels and patterns? (Chapter 6)
- How do group results translate to the individual patient? (Chapter 7)

Chapter 8 summarizes the main research findings with respect to the above topics and attempts to place them in a larger perspective. In addition it discusses limitations of the studies and possible future research directions.

REFERENCES

- Antonuccio, D. O., Danton, W. G., DeNelsky, G. Y., Greenberg, R. P., Gordon, J. S., 1999. Raising questions about antidepressants. *Psychother Psychosom* 68(1), 3-14.
- Barge-Schaapveld, D. Q. C. M., Nicolson, N. A., Berkhof, J., deVries, M. W., 1999. Quality of life in depression: daily life determinants and variability. *Psychiatr Res* 88, 173-189.
- Brandstätter, H., 1994. Well-being and motivational person-environment fit: a time-sampling study of emotions. *European Journal of Personality* 8, 75-93.
- Bronfenbrenner, U., 1979. *The ecology of human development*. Harvard University Press, Cambridge, MA.
- Brown, W. A., Dornseif, B. E., Wernicke, J. F., 1988. Placebo response in depression: a search for predictors. *Psychiatry Research* 26, 259-264.
- Cantor, N., Norem, J., Langston, C., Zirkel, S., Fleeson, W., Cook-Flannagan, C., 1991. Life tasks and daily life experience. *Journal of Personality* 59(3), 425-451.
- Csikszentmihalyi, M., 1990. *Flow: the psychology of optimal experience*. Steps toward enhancing the quality of life. Harper Perennial, New York.
- Csikszentmihalyi, M., Larson, R., 1987. Validity and reliability of the Experience Sampling Method. *J Nerv Ment Dis* 175(9), 526-537.
- Csikszentmihalyi, M., Larson, R., Prescott, S., 1977. The ecology of adolescent activity and experience. *Journal of Youth and Adolescence* 6, 281-294.
- Delespaul, P. A. E. G., 1992. Technical note: devices and time-sampling procedures. In: deVries, M. W. (Ed.), *The Experience of Psychopathology: Investigating Mental Disorders in Their Natural Settings*. Cambridge University Press, Cambridge, pp. 363-373.
- Delespaul, P. A. E. G., 1995. *Assessing Schizophrenia in Daily Life: The Experience Sampling Method*. Ph.D. Dissertation, Maastricht University, Universitaire Pers, Maastricht.
- Delespaul, P. A. E. G., deVries, M. W., 1987. The daily life of ambulatory chronic mental patients. *Journal of Nervous and Mental Disease* 175(9), 537-544.
- deVries, M. W., 1987. Investigating mental disorders in their natural settings. *Journal of Nervous and Mental Disease* 175(9), 509-513.
- deVries, M. W., 1992a. *The Experience of Psychopathology: Investigating Mental Disorders in Their Natural Settings*. Cambridge University Press, Cambridge.
- deVries, M. W., 1992b. Practical issues in psychiatric applications of ESM. In: deVries, M. W. (Ed.), *The Experience of Psychopathology: Investigating Mental Disorders in Their Natural Settings*. Cambridge University Press, Cambridge, pp. 317-323.
- deVries, M. W., 1997. Recontextualizing psychiatry: toward ecologically valid mental health research. *Transcultural Psychiatry* 34(2), 185-218.
- deVries, M. W., Delespaul, P. A. E. G., Dijkman-Caes, C. I. M., 1987. Affect and anxiety in daily life. In: Racagni, G., Smeraldi, E. (Eds.), *Anxious depression: assessment and treatment*. Raven Press, New-York, pp. 21-32.
- Diener, E., Sandvik, E., Pavot, W., Gallagher, D., 1991. Response artifacts in the measurement of subjective well-being. *Social Indicators Research* 24, 35-56.
- Dijkman-Caes, C. I. M. (1993). *Panic disorder and agoraphobia in daily Life*. Ph.D. Dissertation, Maastricht University, Universitaire Pers, Maastricht.
- Faries, D., Herrera, J., Rayamajhi, J., DeBrot, D., Demitrack, M., Potter, W. Z., 2000. The responsiveness of the Hamilton Depression Rating Scale. *J Psychiatr Res* 34(1), 3-10.
- Feist, G. J., Bodner, T. E., Jacobs, J. F., Miles, M., Tan, V., 1995. Integrating top-down and bottom-up structural models of subjective well-being: a longitudinal investigation. *Journal of Personality and Social Psychology* 68(1), 138-150.

- Gibbons, R. D., Clark, D. C., Kupfer, D. J., 1993. Exactly what does the Hamilton Depression Rating Scale measure? *J Psychiatr Res* 27(3), 259-273.
- Hamilton, M., 1960. A rating scale for depression. *Neurol Neurosurg Psychiatr* 23, 56-62.
- Headey, B., Veenhoven, R., Wearing, A., 1991. Top-down versus bottom-up theories of subjective well-being. *Social Indicators Research* 24(1), 81-100.
- Hormuth, S. E., 1986. The sampling of experience in situ. *Journal of Personality* 54(1), 262-293.
- Hurlburt, R. T., Melacon, S. M., 1987. Goofed-up images: thought sampling with a schizophrenic woman. *Journal of Nervous and Mental Disease* 17(9), 575-578.
- Juster, F. T., Stafford, F. P., 1985. Time, goods and well-being. Institute for Social Research, The University of Michigan, Ann Arbor.
- Kahneman, D., Diener, E., Schwarz, N., 1999. Well-being: The foundations of hedonic psychology. Russell Sage Foundation, New York.
- Kaplan, C. D., 1992. Drug craving and drug use in the daily life of heroin addicts. In: deVries, M. W. (Ed.), *The Experience of Psychopathology: Investigating Mental Disorders in Their Natural Settings*. Cambridge University Press, Cambridge, pp. 193-218.
- Katz, M. M., 1998. Need for a new paradigm for the clinical trials of antidepressants. *Neuropsychopharmacol* 19(6), 517-522.
- Kirsch, I., Sapirstein, G., 1998. Listening to Prozac but hearing placebo: a meta-analysis of antidepressant medication. *Prevention & Treatment* 1(Article 0002a).
- Klinger, E., Barta, S., Maxeimer, M., 1980. Motivational correlates of thought content, frequency and commitment. *Journal of Personality and Social Psychology* 39, 1222-1237.
- Kraan, H., Meertens, H., Hilwig, M., Volovics, L., Dijkman-Caes, C. I. M., Portegijs, P., 1992. Selecting measures, diagnostic validity and scaling in the study of depression. In: deVries, M. W. (Ed.), *The Experience of Psychopathology: Investigating Mental Disorders in Their Natural Settings*. Cambridge University Press, Cambridge, pp. 324-338.
- Lance, C. E., Lautenschlager, G. J., Sloan, C. E., Varca, P. E., 1989. A comparison between bottom-up, top-down, and bidirectional models of relationships between global and life facet satisfaction. *Journal of Personality* 57(3), 601-624.
- Lehman, A. F., Burns, B., 1990. Severe mental illness in the community. In: Spilker, B. (Ed.), *Quality of Life Assessments in Clinical Trials*. Raven Press, New York, pp. 357-366.
- Leon, A. C., Marzuk, P. M., Portera, L., 1995. More reliable outcome measures can reduce sample size requirements. *Arch Gen Psychiatry* 52(10), 867-871.
- Leon, A. C., Shear, M. K., Portera, L., Klerman, G. L., 1993. Effect size as a measure of symptom-specific drug change in clinical trials. *Psychopharmacol. Bull.* 29(2), 163-167.
- Litt, M. D., Cooney, N. L., Morse, P., 1998. Ecological momentary assessment (EMA) with treated alcoholics: methodological problems and potential solutions. *Health Psychol* 17(1), 48-52.
- Massimini, F., Carli, M., 1988. The systematic assessment of flow in daily life experience. In: Csikszentmihalyi, M., Csikszentmihalyi, I. (Eds.), *Optimal experience: psychological studies of flow in consciousness*. Cambridge University Press, New-York, pp. 266-287.
- Massimini, F., Csikszentmihalyi, M., Carli, M., 1992. The monitoring of optimal experience: a tool for psychiatric rehabilitation. In: deVries, M. W. (Ed.), *The Experience of Psychopathology: Investigating Mental Disorders in Their Natural Settings*. Cambridge University Press, Cambridge, pp. 270-279.
- Milbrath, L. W., 1982. A conceptualization and research strategy for the study of ecological aspects of the quality of life. *Social Indicators Research* 10, 133-157.
- Montgomery, S. A., 1999. Alternatives to placebo-controlled trials in psychiatry. ECNP Consensus Meeting, September 26, 1996, Amsterdam. European College of Neuropsychopharmacology. *Eur Neuropsychopharmacol* 9(3), 265-269.
- Myin-Germeys, I., Delespaul, P. A., deVries, M. W., 2000. Schizophrenia patients are more emotionally active than is assumed based on their behavior. *Schizophr Bull* 26(4), 847-854.

- Nicolson, N. A., 1992. Stress, coping and cortisol dynamics in daily life. In: deVries, M. W. (Ed.), *The experience of psychopathology: investigating mental disorders in their natural settings*. Cambridge University Press, Cambridge, pp. 219-232.
- Portegijs, P. J. M., 1996. Somatization in frequent attenders of general practice. Unpublished PhD dissertation, University Maastricht.
- Schatzberg, A. F., Kraemer, H. C., 2000. Use of placebo control groups in evaluating efficacy of treatment of unipolar major depression. *Biol Psychiatry* 47(8), 736-744.
- Shiffman, S., Elash, C. A., Paton, S. M., Gwaltney, C. J., Paty, J. A., Clark, D. B., Liu, K. S., Di Marino, M. E., 2000a. Comparative efficacy of 24-hour and 16-hour transdermal nicotine patches for relief of morning craving. *Addiction* 95(8), 1185-1195.
- Shiffman, S., Johnston, J. A., Khayrallah, M., Elash, C. A., Gwaltney, C. J., Paty, J. A., Gnys, M., Evoniuk, G., DeVeaugh-Geiss, J., 2000b. The effect of bupropion on nicotine craving and withdrawal. *Psychopharmacology (Berl)* 148(1), 33-40.
- Smyth, J. M., Soefer, M. H., Hurewitz, A., Stone, A. A., 1999. The effect of tape-recorded relaxation training on well-being, symptoms, and peak expiratory flow rate in adult asthmatics: a pilot study. *Psychology and Health* 14, 487-501.
- Stone, A. A., Shiffman, S. S., DeVries, M. W., 1999. Ecological Momentary Assessment. In: Kahneman, D., Diener, E., Schwarz, N. (Eds.), *Well-being: the foundations of hedonic psychology*. Russell Sage Foundation, New York, pp. 26-39.
- Thase, M. E., 1999. How should efficacy be evaluated in randomized clinical trials of treatments for depression? *J Clin Psychiatry* 60(Suppl 4), 23-31; discussion 32.
- Trivedi, M. H., Rush, H., 1994. Does a placebo run-in or a placebo treatment cell affect the efficacy of antidepressant medications? *Neuropsychopharmacology* 11(1), 33-43.
- van Eck, M., 1996. Stress, Mood, and Cortisol Dynamics in Daily Life. Ph.D. Dissertation, Maastricht University, Universitaire Pers, Maastricht.
- Veenhoven, R., 1991. Is happiness relative? *Social Indicators Research* 24(1), 1-34.
- Wilson, K. C. M., Hopkins, R., deVries, M. W., Copeland, J. R. M., 1992. Research alliance and the limit of compliance: Experience Sampling with the depressed elderly. In: deVries, M. W. (Ed.), *The Experience of Psychopathology: Investigating Mental Disorders in Their Natural Settings*. Cambridge University Press, Cambridge, pp. 339-346.

PART II
PRELIMINARY STUDY (STUDY 1)

CHAPTER 3

**Changes in daily life experience associated with
clinical improvement in depression**

Barge-Schaapveld, D. Q. C. M., Nicolson, N. A., Gerritsen van der Hoop, R., deVries, M. W., 1995. Changes in daily life experience associated with clinical improvement in depression. *Journal of Affective Disorders* 34, 139-154.

Changes in daily life experience associated with clinical improvement in depression

Changes in depressed outpatients' experience of daily activities after 6 weeks of antidepressant treatment were assessed with the Experience Sampling Method (ESM). On the Sickness Impact Profile, treatment responders ($\text{HDRS} \leq 7$, $N = 12$) improved more than non-responders ($N = 9$) in the domains of household chores, leisure and social activities. On ESM measures completed 10 x each day for 6 days pre- and posttreatment, responders showed greater increases in time spent in chores and greater decreases in passive leisure time than non-responders. Responders showed greater increases in positive affect and greater decreases in negative affect during all activities. Thus, ESM provides quantitative evidence of changes in real life time use and subjective experience accompanying clinical improvement.

INTRODUCTION

Although the symptoms of depression have been discussed for centuries (Hare, 1991), it is only in the last decades that the impact of these symptoms on the everyday functioning and well-being of the patient has been recognized (Hammen, 1990; Revicki and Murray, 1994). In recent years the burden of this mood disorder has been well documented for several life domains such as social, productive and leisure activities. Impaired social functioning, such as reduction in frequency and intensity of social contacts, has been reported extensively in depressed patients (De Lisio et al., 1986; Gotlib, 1990; Agosti et al., 1991). This social maladjustment has been viewed as a common consequence of depression, which may persist long after patients are symptomatically recovered (Paykel et al., 1978; Tweed, 1993). Depression is also associated with pronounced disturbances in work (De Lisio et al., 1986; Mintz et al., 1992). In a prospective epidemiological survey, Broadhead et al. (Broadhead et al., 1990) found that major depression carries a high risk of disability days and days lost from work. Although less systematic information is available on impairment in unpaid work such as household

chores and maintenance, it appears that performance of household roles is also disturbed as a consequence of depression (De Lisio et al., 1986). Finally, maladjustment is evident in leisure activities. The performance of leisure requires the exertion of personal initiative and may reflect central hedonic function, which may explain why impairments in this domain are especially likely to persist after clinical remission (De Lisio et al., 1986).

In spite of the numerous antidepressant drug trials conducted, little is known about how clinical improvement is reflected in daily functioning and well-being. In an attempt to address this issue, recent studies have incorporated questionnaire measures of well-being or life satisfaction (Revicki et al., 1992; Rost et al., 1992; Stoker et al., 1992; Tuynman-Qua et al., 1992; Endicott et al., 1993). A major limitation of such cross-sectional measures is that they are unable to obtain unbiased quantitative information on daily life contexts and activities, which may be fundamental for an understanding of patients' subjective experience. In this regard, a time-based method such as the Experience Sampling Method (ESM) may have more potential. ESM uses repeated self-assessments to study the variability of patients' thoughts, mood, motivation, physical symptoms and activities in their natural settings (deVries, 1987). By collecting self-reports from subjects immediately after repeated, random signals, ESM has important advantages over cross-sectional instruments (Verbrugge, 1980; Wheeler and Reis, 1991). First of all, a time-based method reduces recall errors, a particularly important advantage in depression, where retrospective memory bias has been documented (McLeod et al., 1990). Another advantage of a time-based method is its ability to elicit reports of symptoms that are too minor or transient to be captured in a cross-sectional report later, but that may nevertheless be significant to the patient at the time of occurrence. Finally, by providing a longitudinal series of data for each individual, a time-based method offers a rich potential for the analysis of individual variability and change over time.

ESM has been applied in a variety of psychiatric populations (deVries, 1992). Information concerning compliance, reliability and validity of ESM have been reported elsewhere (Csikszentmihalyi and Larson, 1987; deVries, 1987). Previous studies in depression have shown ESM to distinguish between depressed adolescents and their non-depressed peers on time-budgets, mood lability and reactivity to daily life contexts (Merrick, 1992), and to differentiate between groups with different levels of depression severity on measures of mood states (Kraan et al., 1992). The current study is the first application of ESM in the context of a clinical drug trial.

This paper describes how clinical improvement, possibly accompanied by side effects, following antidepressant therapy (fluvoxamine or amitriptyline) is reflected in aspects of depressed patients' daily life experience. In order to better contrast the effects of clinical improvement, we distinguish two groups of patients: responders to treatment and non-responders. We first identify the life domains in which changes in sick-

ness impact as measured with a cross-sectional instrument, the Sickness Impact Profile (SIP), differentiate treatment responders from non-responders. A second question focuses specifically on these life domains and examines the pre- to post-treatment changes in daily life experience associated with clinical improvement. For this purpose, ESM measures of time use, positive and negative affect in daily life are first defined. A third question addresses whether responders to treatment show any changes in daily life domains as assessed with ESM that the SIP fails to pick up. A final question addresses the relationships between SIP life domains and ESM measures of daily life experience.

We hypothesized that improvement in a SIP life domain would be associated with increased time spent (during ESM sampling) in demanding activities and decreased time spent in non-demanding activities related to this domain. Since depression is not only characterized by a persistent and pervasive low mood (American Psychiatric Association, 1987) but also by 'anhedonia', the absence of positive affect (Tellegen, 1985; Clark and Watson, 1988; Watson et al., 1988; Snaith, 1993), we hypothesized that improvement in a life domain as identified by the SIP would be associated with both higher positive affect and lower negative affect during these activities. Furthermore, we hypothesized that ESM measures would be able to identify more subtle changes in daily life experience than a cross-sectional measure, the SIP. Finally, we hypothesized that, since the SIP purports to measure behavior rather than mood (Bergner et al., 1981), ESM time use would be more highly associated with SIP measures than would ESM mood measures.

METHODS

Study design

The study was conducted in five primary care practices in the Netherlands. Subjects, who ranged in age from 18 to 65 years, met DSM-III-R criteria for Major Depressive Disorder (American Psychiatric Association, 1987) and were free of other major psychiatric or medical conditions. For inclusion, patients had to score at least 18 on the 17-item version of the Hamilton Depression Rating Scale (HDRS, Hamilton, 1960) and 4 on the Clinical Global Impression (CGI, Guy, 1976) severity score at Baseline. Ethical committee approval was obtained prior to patient entry. The physicians and the research nurse were trained in diagnosing Major Depressive Disorder, in administering the scales and in using ESM. The study procedures were explained to all patients and their informed consent to participate obtained. Following a one-week placebo run-in period, patients were randomized and tapered-on to either fluvoxamine (first week 50 mg once daily, thereafter 50 mg b.i.d.) or amitriptyline (first week 75 mg once daily, thereafter 75 mg b.i.d.), which they received, single-blind, during six weeks. Two treat-

ments known to differ in side effects profile (Nierenberg and Cole, 1991; Tollefson, 1991; Kasper et al., 1992) but not in efficacy were included in the design in order to increase the variability in daily life measures. Because this study focuses explicitly on self-report measures, a double-blind design was not considered to be necessary.

Instruments

Cross-sectional measures were administered as follows: the HDRS was used to measure clinical improvement and was assessed by the physicians on a regular basis. At each visit, the physicians asked their patients whether or not they had experienced any unusual or unwanted signs or symptoms. Only pre- and post-treatment (Day 43) measures are used here. The SIP (Bergner et al., 1981; Read et al., 1987) was administered by the research nurse as a generic Quality of Life (QoL) scale, intended to measure subject's health status independently of the specific disease or condition, at Baseline and at the end of the study. The SIP consists of 12 modules of daily life activities, which can be clustered in a psychological module (emotional behavior, social interaction, alertness behavior and communication) and in a physical module (body care/movement, mobility and ambulation). The five remaining modules (sleep/rest, eating, home management, work and recreation/pastimes) are independent. All scores are given in percentages. Based on all modules, a total score is calculated, which indicates the level of impact the illness has on a patient's life. The higher the score, the higher the impact of the illness and thus the lower the QoL.

ESM was conducted 'pre-treatment' during 6 consecutive days of the placebo week and 'post-treatment' during 6 days of the last (6th) week of active treatment. The wrist-watch was programmed to signal subjects 10 times a day, between 7.30 am and 10.30 pm. At each signal, which will be referred to as a 'beep', subjects were asked to report their thoughts, current activity, physical and social context by way of open questions. Seven-point Likert scale items (with endpoints: 1 = 'not at all' and 7 = 'extremely') were used to assess subjective experience. Mental states were assessed by asking patients to rate current thoughts with the items 'brooding' or 'pleasant', and to indicate to what extent they could concentrate on their current activity. Mood states were assessed with 14 items. Regarding their physical disposition, patients were asked to rate the items 'thirsty', 'hungry', 'sleepy', 'agitated' and 'feeling well'. Satisfaction with activity and social context was measured by questions such as 'Would you prefer to be doing something else (than the activity you were doing)?' or 'Would you prefer to be alone (when in a social context)?' To determine the elapsed time between the 'beep' and the ESM report (response time), subjects also recorded the time at which the self-report form was completed.

In addition, patients completed short questionnaires concerning sleep patterns each morning, upon waking. This information included the time they went to bed on the

prior evening, the time they required to fall asleep, the number of times they awoke during the night and the time they got up. Patients were also asked to rate on a Likert scale (with endpoints: 1='very poorly' to 7='very well') how well they had slept the night before.

Each sampling period was preceded by a briefing session, during which the research nurse instructed the patient on the sampling procedures and the use of the watch. At the end of each sampling period a debriefing session was held during which the research nurse obtained information from the patient as to the representativeness of the sampled days as well as any experimental effects or annoyance ESM might have caused.

Analysis

Definition of clinical improvement. The aim of this study was to describe the relationship between clinical improvement and changes in daily experience. Due to large individual differences in clinical improvement during the study, we chose to contrast two groups in the analysis. Clinical improvement was therefore defined by a conservative post-treatment HDRS criterion: patients who scored 7 or less on the HDRS at Day 43 were classified as responders and those with a higher post-treatment HDRS score were classified as non-responders (Murphy et al., 1985).

Analysis of ESM data. ESM self-reports completed more than 15 minutes after the signal (4%) were discarded prior to analysis. ESM time use was defined as the percentage of total beeps engaged in each category of activity. Responses to the open question about current activity were first coded into one of 48 categories (e.g. shopping, child care, conversation). In other ESM studies, inter-coder reliability of these activity codings has been found to be acceptable. Activities were subsequently grouped into five larger categories: chores, leisure, social, work and other time use. The category 'chores' consisted of activities such as 'household maintenance' and 'shopping'. The category 'leisure' was differentiated in two sub-categories: active (e.g. sports, hobbies) and passive (e.g. T.V. watching, reading) leisure activities. Social time use included activities such as conversation and visits to and from others. Work consisted of both paid and volunteer work as well as study, whereas the remaining time use category 'other' comprised activities such as transportation and personal hygiene.

In accordance with current models of mood (Tellegen, 1985; Watson and Tellegen, 1985) and supported by principal components analysis with varimax rotation over the averaged mood item scores per subject as well as over total mood item beep scores, two affect scales were formed. Ratings on the Likert-scale items 'happy', 'satisfied', 'relaxed', 'calm', 'energetic' and 'enthusiastic' were averaged to form a positive affect (PA) scale (over all beeps; Cronbach's $\alpha = .88$). The items 'angry', 'irritated', 'anxious', 'sad', 'depressed' and 'lonely' were averaged to form a negative affect (NA) scale (over all

beeps; Cronbach's $\alpha = .87$). Scores were computed as the sum of all items divided by the number of items in the scales and, thus, ranged from 1 to 7.

PA during daily activities was defined in two ways. First, PA scores were averaged for each subject and for each period (pre- and post-treatment) per main activity category. Second, PA during daily activities was assessed by the frequency of highly positive affective states ($PA \geq 5$ on the 7-point scale). The frequency of these beeps was then calculated per activity as a percentage of the subject's total number of beeps spent in that activity. NA during daily activities was similarly measured in two ways: average NA and the frequency of highly negative affective states ($NA \geq 5$). Here again, the frequency of these states was calculated per activity as a percentage of the subject's total number of beeps spent in that activity.

Based on the sleep information collected each morning, four additional ESM measures were defined: duration of sleep (the interval between the time the patient went to bed the prior evening and the time he/she got up the following morning), sleep latency (the interval between going to bed and falling asleep), the number of times the patient awoke during the night and the quality of the patient's sleep. For each subject, a pre-treatment and a post-treatment mean were calculated for each of the above measures, over the 6 days sampled in each period.

Statistical tests. Only subjects who completed both pre- and post-treatment sampling periods were included in the analysis (see 'Patient characteristics' below for information concerning drop-outs).

Within-subject pre- to post-treatment change was tested using the Wilcoxon signed rank sum test. Differences between responders and non-responders were tested with the Mann-Whitney U test for the continuous variables and with the Fisher's exact test for the categorical variables. For the relationships between the SIP life domains and ESM daily life measures, as well as for the associations between the ESM time use and mood measures, Spearman correlations were calculated. All statistical tests were two-tailed. Analyses were performed with SPSS.

RESULTS

Patient characteristics

Of the 25 patients screened, 21 completed the study. Two patients dropped out after the pre-treatment sampling period due to adverse events not related to treatment and two due to difficulties complying with ESM procedures during the first sampling period. Drop-outs were significantly older than completers, with a mean age of 50.5 versus 36.4 years (Mann-Whitney, $p \leq .01$), but did not differ on other

socio-demographic parameters. Although no statistical difference in severity of depression was found between completers and drop-outs, the two subjects who had difficulties with ESM procedures scored relatively higher on the HDRS (26 and 34) at Screening.

Eleven of the 21 completers received fluvoxamine and ten received amitriptyline. No statistically significant differences were found between the two treatment groups on any socio-demographic characteristics, or on any pre- or post-treatment clinical measures (HDRS and CGI). Five out of the ten patients who received amitriptyline reported side effects at some point in the first 4 weeks of treatment (four in Week 1, five in Week 2 and one during Weeks 3-4) with complaints of dry mouth ($N = 3$), dullness or fatigue ($N = 4$), depersonalization ($N = 1$), or headache ($N = 2$). Three out of the eleven patients who were treated with fluvoxamine reported side effects at some time in the first 4 weeks of treatment (one in Week 1, three in Week 2 and two during Weeks 3-4) with complaints of nausea or vomiting ($N = 2$), headache ($N = 1$), dry mouth ($N = 1$) or transpiration ($N = 1$). During Weeks 5-6 (including the ESM sampling period in Week 6), no subjects reported side effects to the physicians. Thus, no differential effects of treatment on daily life measures were to be expected. Therefore we felt justified in combining the two treatment groups in the analysis.

Based on the criterion for treatment response (post-treatment HDRS ≤ 7), twelve completers were classified as responders and nine as non-responders to treatment. No significant difference was found in the sex distribution of the two groups (8 out of 12 responders versus 4 out of 9 non-responders were female). Responders were older than non-responders (mean age: 39.6 versus 32.3; Mann-Whitney, $p \leq .05$) and tended more often to be married (Fisher's exact test, $p = .06$). Responders and non-responders had received similar levels of education. No differences were found in employment status; of the total sample, 43% received either unemployment or sickness benefits, 38% had paid employment, and 19% were housewives.

Pre- and post-treatment HDRS ratings for all subjects are shown in Figure 1. Responders and non-responders to treatment did not differ in severity of depression at Baseline; responders had a mean HDRS score of 24.8 and non-responders of 25.7. After 6 weeks of treatment, HDRS scores had decreased on average by 20.4 to 4.4 for responders and by 9.8 to 15.9 for non-responders, a significant improvement (Wilcoxon, $p \leq .01$) in both cases. However, the improvement was significantly greater in responders than non-responders (Mann-Whitney, $p \leq .001$).

Changes in SIP life domain measures

Changes in SIP modules were first examined to determine which life domains were most relevant to explore with ESM data. As shown in Table 1, responders' overall qual-

ity of life, as measured by the SIP total score, improved significantly following the six weeks of antidepressant treatment. Non-responders' total SIP scores also improved, but significantly less so than those of responders. For the psychological impact modules, similar patterns were observed: both responders and non-responders showed improvement, but, for the total psychological module score as well as for the social interaction sub-module, positive change was significantly greater in responders than in non-responders. In contrast, no differences between responders and non-responders were found in the physical modules (total or sub-modules). For the remaining SIP modules, responders improved significantly more than non-responders in home management chores and leisure activity domains. Between-group differences in 'sleep/rest' improvement failed to reach significance. No differences in improvement were found between responders and non-responders for 'work' or 'eating' modules. In the case of work, it should be noted that a minority of subjects (38%) had paid employment and therefore no differences between responders and non-responders were expected.

To summarize, clinical improvement was most clearly reflected in the domains of social interaction, home management and recreational activity. These areas were therefore selected for further investigation with ESM data.

Changes in ESM measures

Compliance and patient evaluation of ESM

Of the maximum possible 2520 ESM self-reports for these 21 subjects, 81% were completed, with no significant difference between responders (84%) and non-responders (77%). There were no differences either pre- versus post-treatment in the average number of beeps completed. The lowest number of beeps was 28 in the first sampling period and 33 in the second sampling period. Furthermore, responders and non-responders to treatment did not differ in the first sampling period as to the mean delay between the beep and the response time (3.56 versus 4.44 minutes, *ns*). Nevertheless, responders showed a significant decrease in the mean delay in the second sampling period (3.56 pre- versus 2.87 minutes post-treatment, Wilcoxon, $p \leq .05$). No significant change was found in non-responders (4.44 pre- versus 4.08 minutes post-treatment).

Information collected during the debriefing interview suggested that the ESM procedure had relatively little effect on patients' daily experience during either of the two sampling periods. A few subjects reported that participation in the study had some effect on their mood (pre-, post-treatment: 5, 4 subjects), activities (2,2), social contacts (5,4), or thoughts (9,5). Pre-treatment, 11 subjects reported that the ESM procedure was to some extent disruptive or annoying; this was reported by only 6 subjects post-treatment. There were no differences between responders and non-responders on any of the above evaluations.

TABLE 2. Time use (expressed as % of total ESM reports) for responders and non-responders pre- and post-treatment.

Activity category	Responders (N=12)			Non-responders (N=9)			Change in responders > non-responders
	Pre	Post	Significance of change	Pre	Post	Significance of change	
Chores	29.6	34.3	-	28.1	22.4	-	*
Leisure	31.0	23.7	$p=.06$	28.1	34.9	-	*
Active leisure	10.6	10.2	-	4.5	7.5	-	-
Passive leisure	20.4	13.5	*	23.5	27.4	-	*
Social	19.0	19.1	-	23.8	16.2	-	-

* $p \leq .05$

Total for each group pre- and post-treatment does not add up to 100% as time use categories 'work' and 'other' are left out.

ESM time use

We first tested whether the improvements found with the SIP for household chores, leisure activities and social interactions were reflected in changes in time spent in these activities as estimated with the ESM data. As shown in Table 2, responders increased the time they spent on household chores by 5% following treatment while non-responders decreased their household activities by 6%. Furthermore, responders showed a tendency to decrease the time spent in leisure activities, which differed from the pattern of change observed in non-responders.

A further breakdown into active and passive leisure time revealed that responders spent significantly less time in passive leisure activities, such as doing nothing, watching T.V. or reading a newspaper, following the 6 weeks of treatment in both absolute terms and in comparison to non-responders. The percentage of time spent in active leisure, on the other hand, remained more or less constant over the two sampling periods for both groups. Finally, the percentage of time spent in social interactions, comprising activities such as conversations, visits to and from family and meals with friends, did not change significantly for either responders or non-responders from pre- to post-treatment, and no significant between-group difference was found.

ESM mood measures

Positive affect. No difference was found between responders (mean = 2.86, SD = .75) versus non-responders (mean = 2.66, SD = .58) during the first sampling period in average PA over all activities. Following the six weeks of treatment, responders had higher PA (change: +1.30, $p \leq .01$), whereas change in PA in non-responders (+0.17) was not significant.

The average PA calculated separately for each type of activity increased significantly in responders compared to non-responders during all three main activity categories: chores ($p \leq .05$), leisure ($p \leq .05$) and social activities ($p \leq .01$). These data are shown in the top half of the graphs in Figure 2. Within leisure activities, PA improvement was significantly greater in responders than non-responders for passive ($p \leq .05$) but not for active leisure.

Negative affect. Pre-treatment, responders (mean = 2.53, SD = 1.01) did not differ from non-responders (mean = 3.06, SD = .93) in average NA over all activities. Following the six weeks of treatment, responders had lower NA (change: -1.15 , $p \leq .01$), whereas change in NA in non-responders (-0.16) was not significant.

Average NA in responders decreased significantly when compared to non-responders (chores: $p \leq .05$; leisure and social: $p \leq .01$). These data are shown in the bottom half of the graphs in Figure 2. Again a breakdown of leisure activities revealed greater NA improvement in responders than non-responders for passive but not for active leisure.

Highly positive states. Both responders and non-responders had 1% of highly positive states during the first sampling week pre-treatment. Although it remained at this level for non-responders post-treatment, this percentage increased significantly to 34% (Wilcoxon, $p \leq .01$; Mann-Whitney, $p \leq .05$) in responders following the 6 weeks of treatment.

Results found for the frequency of highly positive states during the various activities were similar to the results found with the mean PA. Although the rate of occurrence of highly positive states pre-treatment was about 1% for both responders and non-responders during the various activities (top half of graphs in Figure 3), it increased in responders to 34% for chores, to 42% for leisure activities and to 31% for social interactions. These changes were all significant (leisure: $p \leq .05$; chores and social: $p \leq .01$) when compared to non-responders, who remained around the 1% level for all three activities. Here again, within leisure activities, responders experienced a highly positive state significantly more frequently during passive (but not during active) leisure than non-responders.

Highly negative states. No difference was found in the percentage of highly negative affective states responders (4%) and non-responders (10%) experienced over all activities pre-treatment. Nor was there a group difference in the change in percentage of highly negative states following treatment (responders: -4% ; non-responders: $+1\%$).

The pre- to post-treatment change in the percentage of highly negative states patients experienced during each particular activity was not significant in either responders or non-responders. Although the percentage of highly negative states experienced by responders was already low pre-treatment, individuals in this group showed no highly negative states at all post-treatment.

FIGURE 2. Mean positive and negative mood scale scores in responders and non-responders pre- and posttreatment. Error bars, SEM.

Correlations between ESM measures over all subjects. Changes in average PA and average NA showed a negative association ($r = -.61, p \leq .01$). An increase in average PA was accompanied by a greater frequency of high positive states ($r = .81, p \leq .001$) and, although an increase in average NA was also accompanied by a greater frequency of high negative states, the latter association was weaker ($r = .51, p \leq .05$). Patients who experienced an increase in the frequency of high positive states did not experience a decrease in the frequency of high negative states ($r = .03, ns$). Increases in time spent in one activity category did not automatically result in decreases in another category, in that the analysis did not add up to 100%. Patients who showed the greatest increases in chore time did, however, show the greatest decreases in passive leisure ($r = -.76, p \leq .001$) and the greatest increases in social interactions ($r = .52, p \leq .05$). Changes in social interaction time were negatively associated with changes in active leisure ($r = -.46, p \leq .05$).

FIGURE 3. Mean % of highly positive and highly negative states in responders and non-responders pre- and posttreatment. Error bars, SEM.

The remaining correlations were not significant (changes in passive versus active leisure: $r = .23$; chores versus active leisure: $r = -.36$; passive leisure versus social interaction: $r = -.40$). With the exception of a significant association between general increases in PA and increased time spent in chores post-treatment ($r = .48, p \leq .05$), changes in ESM affect measures were not associated with changes in time use.

Sleep

In order to assess whether responders to treatment showed any changes in daily life domains as assessed with ESM that the SIP failed to pick up, we tested the changes in ESM sleep measures. Average duration of sleep, delay in falling asleep and number of awakenings during the night did not change significantly following the six weeks of treatment in either responders or non-responders. However, responders rated the quality of their sleep to be higher post-treatment (5.3 versus 4.5 pre-treatment, Wilcoxon, $p \leq .05$). This change was significant ($p \leq .05$) when compared to the change in

non-responders' quality of sleep (from 3.8 pre-treatment to 3.4 post-treatment), although the two groups did not differ on this aspect pre-treatment.

Relationship between SIP and ESM measures

In an attempt to identify the relationships between SIP life domains and ESM measures of daily life experience, Spearman correlations between the pre- to post-treatment change scores of the SIP modules (household chores, leisure and social interactions) and the pre- to post-treatment change scores of the logically related ESM variables, namely the estimated time use, the two measures of PA felt during daily activities as well as the two measures of NA were calculated. All correlations between the SIP and the ESM positive affect measures were expected to be negative, as higher SIP scores reflect poorer quality of life. Consequently, correlations between the SIP and the ESM negative affect measures were expected to be positive. The highest correlations, negative in direction, were expected to occur between the SIP modules and ESM estimated time use, as most SIP items asked specifically about the frequency of activities performed (e.g. 'I am going out for entertainment less').

The correlations revealed a pattern of negative associations between the SIP scores and the ESM positive affect measures, with significant correlations found for mean PA. As predicted, measures of negative affect in daily activities were positively associated with SIP scores, and highly significant for mean NA. However, contrary to expectations, no or low associations were found between SIP module scores and ESM estimated time use. As predicted, these associations were negative for demanding activities such as chores, social interactions and active leisure and positive for non-demanding activities such as passive leisure.

Correlations between the SIP 'sleep/rest' module and the four ESM sleep measures were expected to be positive for sleep latency and number of awakenings and negative for sleep duration and quality of sleep. All correlations were in the expected direction, except for sleep latency ($r = -.04$, *ns*). The correlations were low (sleep duration: $r = -.25$, *ns*) to moderate (number of awakenings: $r = .44$, $p \leq .05$; quality of sleep: $r = -.55$, $p \leq .01$).

DISCUSSION

In this sample of depressed outpatients, individuals who demonstrated the greatest clinical improvement following 6 weeks of active pharmacological treatment showed greater changes in daily life experience than individuals who improved less. On the SIP, a cross-sectional instrument widely used as a QoL measure, responders improved rela-

TABLE 3. Spearman correlations between change scores on SIP modules and ESM measures ($N=21$).

SIP modules	Time spent in activity	ESM measures			
		Positive mood		Negative mood	
		Mean level	% highly positive states	Mean level	% highly negative states
Chores	-.10	-.39	-.28	.55*	.26
Leisure	.23	-.45*	-.31	.69**	.40
Social	-.08	-.47*	-.37	.67**	.24

* $p \leq .05$, ** $p \leq .01$; Spearman correlations between SIP leisure module and ESM time spent in active leisure: $-.04$ ($N=15$, *ns*). Spearman correlations between SIP leisure module and ESM time spent in passive leisure: $.36$ ($N=21$, *ns*).

tive to non-responders in the domains of household maintenance, leisure and social activities. ESM results clarify the nature of the changes in these three aspects of daily life in terms of quantitative estimates of time actually spent in these activities and accompanying mood states. With respect to time use, treatment responders increased time spent on chores and reduced time spent on passive leisure. Contrary to expectation, responders showed no significant increase in social interaction time. Across all activities except active leisure, responders experienced greater increases in average positive mood and greater decreases in average negative mood than non-responders. Furthermore, during these same activities, responders reported highly positive mood states more often than non-responders; the frequency of extremely negative mood states did not differ between the two groups. Finally, clinical improvement was associated with an increase in daily self-rated sleep quality, whereas differences between responders and non-responders on the SIP sleep module had failed to reach significance.

Time use patterns have been related to well-being (Juster and Stafford, 1985) and would also seem to be relevant to the concept of QoL, in that they reflect the extent to which an individual is interested in and capable of engaging in normal daily activities. In contrast to physician ratings of psycho-social adjustment in various activity domains (e.g. De Lisio et al., 1986; Agosti et al., 1991), time use can be objectively defined and measured in real life. Some existing QoL questionnaires attempt to assess time use indirectly, with global items like 'I sit during much of the day' (SIP) or 'During the past 4 weeks, have you cut down on the amount of time you spent on work or other activities?' (SF-36, Medical Outcomes Study). Studies have shown, however, that retrospective estimates of personal time use are highly inaccurate, even over time periods as short as the past 24 hours (Bernard et al., 1984). Reliable self-report information can only be obtained from time diaries, such as those used in survey research (Szalai et al., 1972; Robinson, 1987), or from time-sampling methods like ESM.

To date, only a few studies (all using ESM) have systematically investigated time use in psychiatric disorders. Previous studies, like our own, suggest that time spent in productive activities and social activities and the balance between active and passive leisure time may be particularly sensitive indicators of clinical state. For example, the within-subject changes in time use we observed following clinical improvement (increased household chore time, decreased passive leisure) are similar to patterns reported by Merrick (Merrick, 1992) in a study comparing daily life experience in currently depressed, previously depressed, and a control group of adolescents. Currently depressed youngsters spent significantly less time on average in productive activities such as schoolwork or a job than either recovered or control subjects. Furthermore, although the three groups did not differ in total leisure time (about 44% of all ESM reports), currently depressed adolescents spent dramatically more time in passive leisure activities (watching television, reading, thinking) and less time in socialising than adolescents in the other two groups. Similarly, in a case study of a woman being treated successfully for agoraphobia, time use patterns derived from nine separate ESM sampling periods over the course of a year showed a gradual decrease in T.V. watching (from 45% to less than 15%), paralleled by an increase in active leisure and social activities (Delle Fave and Massimini, 1988). Due to the influences of a multitude of social and demographic factors on time use, within-subject research designs can be expected to be more sensitive to clinical improvement than between-group comparisons. The fact that significant changes could be detected in our small sample of patients following only 6 weeks of treatment suggests that time use measures may be a feasible and worthwhile addition to standard assessments in clinical trials.

Interpretation of the clinical significance of the time use changes we found in improved depressed outpatients is limited by both the short duration of the study and the lack of normative data. It is thus unclear whether further change might have occurred with more prolonged treatment and whether post-treatment time budgets resembled those of healthy individuals. An accurate general picture of time use patterns in the larger population can be obtained from surveys. From recent Dutch survey data, for example, the average percentage of total (non-sleep) time spent in household chores and passive leisure can be estimated as 23% and 21%, respectively (Netherlands Central Bureau of Statistics, 1988); these figures are roughly comparable to the ESM estimates we obtained for these activities in responders post-treatment (Table 2). Differences in methods of data collection, activity codes, and subject socio-demographic characteristics, however, make meaningful direct comparisons impossible.

Both average positive affect and the frequency of high positive affect states increased significantly in clinically improved versus unimproved subjects. PA increased during activities that became more frequent (i.e., chores), but also during activities that declined in frequency (passive leisure). In the case of chores, patients with the greatest

improvements in positive affect were those most likely to show post-treatment increases in chore time. Although the causal relationship between changes in mood and changes in behavior cannot be determined in a naturalistic study, it seems intuitively more likely that an increase in energy, enthusiasm, and happiness (PA) would precede rather than follow a greater participation in household maintenance. Given the salience of low positive affect in the phenomenology of depression, in particular (Clark and Watson, 1988), and the relevance of both positive and negative affect to the concept of well-being, in general (Diener, 1984), current psychological models of affect should be more widely incorporated into clinical trial and quality of life research designs.

Surprisingly, neither positive nor negative affect varied significantly in relation to the current activity, in either responders or non-responders, pre- or post-treatment. Based on the results of both diary and ESM studies, we had expected to find higher positive and lower negative affect during leisure activities and social interactions than during chores, at least in subjects who showed clinical improvement. Previous studies of healthy individuals report an association between activities and subjective states, ranging from self-esteem (Wells, 1988), motivation (Csikszentmihalyi and Larson, 1987), challenge and skills (Massimini et al., 1987), enjoyment (Robinson, 1977) to affect (Kubey and Csikszentmihalyi, 1990). It is possible that the absence of activity-specific mood variability in our study reflects an aspect of depression that failed to normalize after 6 weeks of treatment. Alternatively, the activity categories we used may have been too broad, or the sample size too small, for detecting associations with mood. Future studies incorporating normal control subjects will help clarify this issue.

Daily ESM assessments of sleep were related to the SIP sleep module but were apparently more sensitive to changes associated with clinical improvement. Other SIP measures were either conceptually too difficult to relate to ESM variables (e.g. mobility), or were not relevant for a sufficient number of subjects in this outpatient sample (e.g. work). The potential advantages of ESM, in terms of greater sensitivity, over cross-sectional measures in psychiatry needs to be further examined. It should also be noted that many aspects of the ESM data, such as cognition, motivation and social context, remain to be investigated. These are areas where ESM data may eventually be able to expand our understanding of clinical improvement.

We hypothesized that improvement in a SIP life domain, that is a decrease in the SIP score, would be associated with increased time spent (during ESM sampling) in demanding activities and decreased time spent in non-demanding activities related to this domain. In addition, because many of the SIP items are phrased in terms of time use, we expected the SIP scores to correlate more highly with the ESM time use measures than with the ESM measures of affect. Although all correlations were in the expected direction, only the correlations between changes in SIP scores and changes in

average mood measures were significant, while those between SIP scores changes and ESM time use changes were not. A possible explanation is that the mood typically experienced during an activity is both more salient and easier to recall than the frequency with which the activity is performed.

In interpreting these results, it is important to note that the number of subjects in this study was small and that the standard cut-off-point used to classify responders and non-responders was relatively arbitrary, as almost all patients improved. Thus, responders and non-responders were part of a continuum, rather than two distinct groups. In addition, it must be stated that the single-blind design may have introduced biases in both clinical assessment measures (HDRS) and in clinician-rated side effects; however, no differences between the two treatment groups on these measures were found. Moreover, the main results reported here concern self-report measures, which would not be subject to this source of possible bias. Due to the nature of the study design, changes in daily life experience associated with clinical improvement cannot be definitely attributed to pharmacological treatment, since a spontaneous remission may have occurred. This emphasizes the need for a placebo-controlled study to analyse the effects of pharmacological treatment on daily life experience. Finally, given the small sample size and the single-blind design, this study cannot adequately distinguish the effects of different pharmacological treatments on daily life experience. We had expected that the two treatments, because of the differences in described side effects profiles (Nierenberg and Cole, 1991; Tollefson, 1991; Kasper et al., 1992), might be associated with different measures of daily life experience. However, the side effects appeared to have largely disappeared by Week 6. Future studies should include ESM sampling periods at an earlier stage in the treatment in order to better address the effects of antidepressant side effects on patients' daily life experience.

Although cross-sectional measures can detect QoL changes in life domains, the current evidence suggests that a method such as the ESM is required to describe treatment impact in terms of daily life experience. Based on acceptable levels of compliance and procedure effects on mood and behaviour, the current study has shown that depressed outpatients are willing and able to use ESM. While patients were (equally) able to comply both pre- and post-treatment, the finding that responders decreased the response time significantly post-treatment may reflect improvement in concentration or cognitive performance in this subgroup. Although the scope of this paper has been essentially limited to the description of changes in daily life experience associated with clinical improvement in those life domains that show significant changes on the SIP, it has shown that ESM is also capable of revealing subtle changes in daily life experience that are not picked up by a cross-sectional measure such as the SIP.

REFERENCES

- Agosti, V., Stewart, J. W., Quitkin, F. M., 1991. Life satisfaction and psychosocial functioning in chronic depression: effect of acute treatment with antidepressants. *Journal of Affective Disorders* 23(1), 35-41.
- American Psychiatric Association, 1987. *Diagnostic and Statistical Manual of Mental Disorders*, 3rd ed. revised. American Psychiatric Association, Washington, DC.
- Bergner, M., Bobbitt, R. A., Carter, W. B., Gilson, B. S., 1981. The Sickness Impact Profile: development and final revision of a health status measure. *Med Care* 19(8), 787-805.
- Bernard, H. R., Killworth, P., Kronenfeld, D., Sailer, L., 1984. The problem of informant accuracy: the validity of retrospective data. *Annual Review of Anthropology* 13, 495-517.
- Broadhead, W. E., Blazer, D. G., George, L. K., Tse, C. K., 1990. Depression, disability days, and days lost from work in a prospective epidemiologic survey. *J. Am. Med. Ass.* 264(19), 2524-2528.
- Clark, L. A., Watson, D., 1988. Mood and the mundane: relations between daily life events and self-reported mood. *Journal of Personality and Social Psychology* 54(2), 296-308.
- Csikszentmihalyi, M., Larson, R., 1987. Validity and reliability of the Experience Sampling Method. *J Nerv Ment Dis* 175(9), 526-537.
- De Lisio, G., Maremmanni, I., Perugi, G., Cassano, G. B., Deltiro, J., Akiskal, H. S., 1986. Impairment of work and leisure in depressed outpatients: a preliminary communication. *J Affect Disord* 10, 79-84.
- Delle Fave, A., Massimini, F., 1988. Modernization and the changing contexts of flow in work and leisure. In: Csikszentmihalyi, M., Csikszentmihalyi, I. (Eds.), *Optimal experience: psychological studies of flow in consciousness*. Cambridge University Press, New-York, pp. 193-213.
- deVries, M. W., 1987. Investigating mental disorders in their natural settings. *Journal of Nervous and Mental Disease* 175(9), 509-513.
- deVries, M. W., 1992. The experience of psychopathology in natural settings: introduction and illustration of variables. In: deVries, M. W. (Ed.), *The Experience of Psychopathology: Investigating Mental Disorders in Their Natural Settings*. Cambridge University Press, Cambridge, pp. 3-26.
- Diener, E., 1984. Subjective well-being. *Psychological Bulletin* 95(3), 542-575.
- Endicott, J., Nee, J., Harrison, W., Blumenthal, R., 1993. Quality of Life Enjoyment and Satisfaction Questionnaire: a new measure. *Psychopharmacology Bulletin* 29(2), 321-326.
- Gotlib, I. H., 1990. An interpersonal systems approach to the conceptualization and treatment of depression. In: Ingram, R. E. (Ed.), *Contemporary Psychological Approaches to Depression*. Plenum Press, New-York, pp. 137-154.
- Guy, W., 1976. *ECDEU Assessment Manual for Psychopharmacology*. US Department of Health, Education and Welfare, Rockville, MD, pp. 59-70.
- Hamilton, M., 1960. A rating scale for depression. *J Neurol Neurosurg Psychiat* 23, 56-62.
- Hammen, C., 1990. Vulnerability to depression: personal, situational and family aspects. In: Ingram, R. E. (Ed.), *Contemporary psychological approaches to depression*. Plenum Press, New-York, pp. 59-70.
- Hare, E., 1991. The history of 'Nervous Disorders' from 1600 to 1840 and a comparison with modern views. *Br. J. Psychiatr.* 159, 37-45.
- Juster, F. T., Stafford, F. P., 1985. *Time, goods and well-being*. Institute for Social Research, The University of Michigan, Ann Arbor.
- Kasper, S., Fuger, J., Moller, H. J., 1992. Comparative efficacy of antidepressants. *Drugs* 43(Suppl. 2), 11-23.
- Kraan, H., Meertens, H., Hilwig, M., Volovics, L., Dijkman-Caes, C. I. M., Portegijs, P., 1992. Selecting measures, diagnostic validity and scaling in the study of depression. In: deVries, M. W. (Ed.), *The Experience of Psychopathology: Investigating Mental Disorders in Their Natural Settings*. Cambridge University Press, Cambridge, pp. 324-338.
- Kubey, R., Csikszentmihalyi, M., 1990. *Television and the Quality of Life: how viewing shapes everyday experience*. Lawrence Erlbaum Associates, Publishers, Hillsdale, New Jersey.

- Massimini, F., Csikszentmihalyi, M., Carli, M., 1987. The monitoring of optimal experience. A tool for psychiatric rehabilitation. *J Nerv Ment Dis* 175(9), 545-9.
- McLeod, J. D., Turnbull, J. E., Kessler, R. C., J.M., A., 1990. Sources of discrepancy in the comparison of a lay-administered diagnostic instrument with clinical diagnosis. *Psychiatry Research* 31(2), 145-159.
- Merrick, W. A., 1992. Dysphoric moods in depressed and non-depressed adolescents. In: deVries, M. W. (Ed.), *The Experience of Psychopathology: Investigating Mental Disorders in Their Natural Settings*. Cambridge University Press, Cambridge, pp. 148-156.
- Mintz, J., Mintz, L. I., Arruda, M. J., Hwang, S. S., 1992. Treatments of depression and the functional capacity to work. *Arch. Gen. Psychiatry* 49(10), 761-768.
- Murphy, G. E., Simons, A. D., Wetzel, R. C., 1985. Plasma nortriptyline and clinical response in depression. *J. Aff. Disorders* 9, 123-129.
- Netherlands Central Bureau of Statistics. (1988). *A Survey on Time Use in The Netherlands*. [In Dutch; with English summary.] .
- Nierenberg, A. A., Cole, J. O., 1991. Antidepressant adverse drug reactions. *J. Clin. Psychiatry* 52(6 (Suppl.)), 40-47.
- Paykel, E. S., Weissman, M. M., Prusoff, B. A., 1978. Social maladjustment and severity of depression. *Comprehensive Psychiatry* 19(2), 121-128.
- Read, J. L., Quinn, R. J., Hofer, M. A., 1987. Measuring overall health: an evaluation of three important approaches. *J. Chron. Dis.* 40(Suppl. 1), 7S-21S.
- Revicki, D. A., Murray, M., 1994. Assessing health-related quality of life outcomes of drug treatments for psychiatric disorders. *CNS Drugs* 1(6), 465-476.
- Revicki, D. A., Turner, R., Brown, R., Martindale, J. J., 1992. Reliability and validity of a health-related quality of life battery for evaluating outpatient antidepressant treatment. *Quality of Life Research* 1(4), 257-266.
- Robinson, J., 1977. *How Americans use time: a social-psychological analysis of everyday behaviour*. Praeger, New York.
- Robinson, J. P., 1987. Microbehavioral approaches to monitoring human experience. *J Nerv Ment Dis* 175, 514-518.
- Rost, K., Smith, G. R., Burnman, M. A., Burns, B. J., 1992. Measuring the outcomes of care for mental health problems: the case of depressive disorders. *Med. Care* 30(Suppl. 5), S266-S273.
- Snaith, P., 1993. Anhedonia: a neglected symptom of psychopathology. *Psychological medicine* 23, 957-966.
- Stoker, M. J., Dunbar, G. C., Beaumont, G., 1992. The SmithKline Beecham 'Quality of Life' scale: a validation and reliability study in patients with affective disorder. *Quality of Life Research* 1(6), 385-395.
- Szalai, A., Converse, P., Feldheim, P., et al., 1972. *The Use of Time*. Mouton, The Hague.
- Tellegen, A., 1985. Structures of mood and personality and their relevance to assessing anxiety, with an emphasis on self-report. In: Tuma, A. H., Maser, J. D. (Eds.), *Anxiety and the anxiety disorders*. Erlbaum, Hillsdale, NJ, pp. 681-706.
- Tollefson, G. D., 1991. Antidepressant treatment and side effect considerations. *J. Clin. Psychiatry* 52(5 (Suppl.)), 4-13.
- Tuynman-Qua, H., Jonghe de, F., McKenna, S., Hunt, S., 1992. *Schaal voor de meting van de kwaliteit van het leven bij depressie*. Ibero Publikaties, Houten.
- Tweed, D. L., 1993. Depression-related impairment: estimating concurrent and lingering effects. *Psychological Medicine* 23(2), 373-386.
- Verbrugge, L. M., 1980. Health Diaries. *Medical Care* 18(1), 73-95.
- Watson, D., Clark, L. A., Carey, G., 1988. Positive and negative affectivity and their relation to anxiety and depressive disorders. *Journal of Abnormal Psychology* 97(3), 346-353.
- Watson, D., Tellegen, A., 1985. Toward a consensual structure of mood. *Psychol Bull* 98, 219-235.
- Wells, A. J., 1988. Variations in mothers' self-esteem in daily life. *J Pers Soc Psychol* 55(4), 661-668.
- Wheeler, L., Reis, H. T., 1991. Self-recording of everyday life events: origins, types, and uses. *Journal of Personality* 59(3), 339-354.

PART III
MAIN STUDY (STUDY 2)

CHAPTER 4

Using ESM to investigate QoL in clinical trials of antidepressants: A methodological overview

Using ESM to investigate QoL in clinical trials of antidepressants: A methodological overview

Study 1 data showed that, with the exception of two subjects (somewhat older and more depressed than the rest), compliance with ESM was high, and the ESM procedure had little effect on patients' daily experience during either of the two sampling periods (see Chapter 3). In addition, results showed that positive mood increased, negative mood decreased, and patterns of time use changed following successful treatment with fluvoxamine or amitriptyline. However, due to the nature of the study design, these changes in daily life experiences could not be definitely attributed to pharmacological treatment, since a spontaneous remission or placebo effects could have occurred. Therefore, Study 2 was initiated with a view to build on the experience and to resolve many of the limitations of Study 1. In the first section the study objectives are described and the differences in design with respect to Study 1 are highlighted. Both the measures and the procedure used in Study 2 are described in a second section, again highlighting the changes made on the basis of the experience obtained in the previous study. Finally, results concerning the use of ESM to investigate QoL in clinical trials of antidepressants are presented.

STUDY OBJECTIVES AND DESIGN

Study 2 investigated the effects of depression and antidepressant treatment (imipramine) on determinants and variability of QoL in daily life, as assessed with ESM. The focus in the current chapter is on the feasibility and utility of ESM in achieving this aim. Two objectives are defined, as follows:

- To assess the feasibility of using ESM in clinical trials in depression by investigating how well depressed patients comply with repeated sampling periods over 18 weeks of treatment.
- To investigate the utility of ESM in clinical trials in depression. In order to be useful in such a context, ESM must yield valid and reliable information about QoL in daily life of depressed patients and about daily life effects of antidepressant treatment. In addition, ESM should be more sensitive to treatment effects than traditional retrospective questionnaires. Sensitivity can be investigated in two ways:
- *Quantitatively*: By how much can ESM, through repeated measurements, increase the statistical power, and thereby reduce the number of subjects required for detecting treatment effects?

- *Qualitatively:* Can ESM deliver new insights about QoL in daily life of depressed patients and daily life effects of antidepressant treatment not obtainable via conventional research methods? (This question is largely addressed in Chapters 5, 6 and 7, and is discussed in Chapter 8. It will not be considered in the current chapter).

In contrast to Study 1, the current study was double-blind and placebo-controlled, so that observed changes in daily life experiences could be attributed with more confidence to the active drug. In addition, time sampling was done more extensively to better assess the impact of side effects on daily life experiences as well as continued improvement of QoL during extended treatment. Finally, a control group was included in this study so that the extent to which daily life experiences were normalized after treatment could be assessed.

METHODS

Subjects

In order to be feasible and useful in the context of clinical trials, ESM should be fully integrated in the logistics surrounding the conduct of trials. Hence, in addition to the usual selection criteria used for the selection of participating sites (i.e., experience with the conduct of depression trials), two aspects were kept in mind: (1) the GP had to be part of a local research network, and (2) location had to be geographically near Maastricht. The first aspect was necessary in order to ensure that the research nurse, who was employed by the research network and trained in ESM, could conduct the briefing and debriefing sessions that were required prior and at the end of each sampling period. The second aspect was regarded as useful in the sense that technical support for the programmed watches was available in Maastricht. Moreover, the timing of the different sampling periods were chosen in such a way that patients were not required to have more GP visits than would usually be the case in such a depression trial. Thus, briefing and debriefing sessions took place at scheduled GP visits.

Depressed patients

Participating patients met criteria for primary moderate or severe Major Depressive Disorder according to DSM-III-R (American Psychiatric Association, 1987), single or recurrent episode, as assessed by the GPs. At the baseline visit, depressed patients had to score 18 or higher on the 17-item version of the HDRS (Hamilton, 1960) and 4 on the CGI severity of illness scale (Guy, 1976). Patients were randomized if they had completed a minimum of 30 ESM self-reports - thus 50% of the maximum possible - during the baseline (pre-treatment) sampling period.

Healthy controls

On the basis of the distribution in socio-demographic characteristics (sex, age, work status, and living circumstances) of each block of four depressed patients included in the study, two healthy controls were recruited. This procedure allowed for a control group that was comparable in socio-demographics to the patient group and comparable in size to each of the two treatment groups. Healthy controls were selected by the same GPs as the patient group, with later exclusion of any with either a current psychiatric disorder or a lifetime history of major depressive disorder, as determined with the Diagnostic Interview Schedule (Dingemans et al., 1985).

Measures

Retrospective measures

Most conventional questionnaires are global and retrospective, in that subjects are asked usually to summarize their experiences or feelings over some period of time, for example the past week or month. The retrospective measures used in Study 2 were chosen on the basis of their conceptual relationship with ESM derived measures. All retrospective measures had a one-week timeframe. In instances where no adequate measure was available, retrospective measures were specifically designed for this study and, thus, no prior data were available on their sensitivity. Measures are listed in Table 1a.

Subjects were asked to rate the quality of their life in the previous week on a visual analogue scale (*QoL VAS*), a 100-mm line with endpoints 'the worst quality of life you can imagine for yourself' and 'the best quality of life you can imagine for yourself' (Andrews and McKennell, 1980). In addition, patients were asked to complete the Dutch version of the Positive Affect and Negative Affect Schedule (PANAS, Peeters et al., 1996), containing two scales, Positive Affect (*PA*) and Negative Affect (*NA*) of 10 items each. The *PA* scale reflects one's level of pleasurable engagement with the environment, whereas the *NA* scale is a general factor of subjective distress (Watson et al., 1988). All items are scored on a 5-point Likert-type scales ranging from (1) 'very slightly or not at all' to (5) 'very much'. Furthermore, based on previous imipramine studies (e.g., Cassano et al., 1994), a list of 10 of the most frequently encountered side effects of imipramine was generated (see Table 1a). For each *complaint*, subjects were asked to indicate *how frequently* it had occurred in the previous week (1 'not at all' to 5 'several times a day') and, if it had occurred, *how troublesome* it was (1 'not at all' to 5 'very'). Finally, patients rated the *frequency* and *enjoyment* they experienced in performing different type of *activities*. All activities reported in Study 1 (see Chapter 3) were ranked per sampling period according to the average frequency with which they were reported across individuals. The 15 most frequently reported activities were the same in the two periods, so that these were chosen to form a list of activities for the current study (see Table 1a). Regarding the previous week, subjects were asked how often they had

TABLE 1. Description of the measures used.

A. Retrospective measures – Self-report

QoL VAS	Rating on 100-mm visual analogue scale (1 <i>worst QoL I can imagine for myself</i> to 100 <i>best QoL I can imagine for myself</i>)
PANAS	Self-rating of affect on two dimensions: Positive Affect = PA (<i>attentive, interested, alert, excited, enthusiastic, inspired, proud, determined, strong, active</i>) Negative Affect = NA (<i>hostile, irritable, guilty, ashamed, nervous, jittery, distressed, upset, afraid, scared</i>) All items are scored on 5-point scales (1 <i>not at all</i> to 5 <i>very</i>)
Complaints	List of 10 most frequent side effects of imipramine: <i>headache, dizziness, dry mouth, nausea, heart palpitations, drowsiness, urinary problems, blurred vision, sweating, constipation</i> Severity: 5-point scale (1 <i>not at all</i> to 5 <i>very</i>) Frequency: 5-point scale (1 <i>not at all</i> to 5 <i>several times a day</i>)
Activities	List of 15 most frequently occurring activities in daily life: <i>household chores, conversation, rest/nap, child care, read book/newspaper, watch TV/listen to radio, work/study, hobbies/sports, shopping, personal care, eating, doing nothing, visit/receive visit, taking a walk, going out</i> Enjoyment: 5-point scale (1 <i>not at all</i> to 5 <i>very much</i>) Frequency: 5-point scale (1 <i>not at all</i> to 5 <i>several times a day</i>)

B. ESM beep measures

mQoL	'In general, how is it going with you right now?' (rated –3 <i>very bad</i> to 3 <i>very good</i>)
PA	Mean of items <i>energetic, cheerful, satisfied, alert, calm, enthusiastic, strong, and happy</i> (rated 1 <i>not at all</i> to 7 <i>extremely</i>)
NA	Mean of items <i>hostile, depressed, tense, lonely, anxious, insecure, guilty, harried, and irritable</i> (rated 1 <i>not at all</i> to 7 <i>extremely</i>)
Complaints	Five 7-point Likert scales for <i>headache, dizziness, dry mouth, drowsiness, and nausea</i> (rated 1 <i>not at all</i> to 7 <i>extremely</i>) Severity: mean rating on the five scales Frequency: percentage of ESM records with mean severity ≥ 2
Current activity	Subject's written response coded and collapsed into 8 categories: <i>work/study, household chores, shopping, childcare, social activities (visits/going out), active leisure (hobbies/sports), passive leisure (watching TV/reading), doing nothing</i> Enjoyment: 'How much are you enjoying this activity?' (1 <i>not at all</i> to 7 <i>extremely</i>) Frequency: percentage of ESM records in which an activity was reported
Disturbance	Level of disturbance by the 'beep' (1 <i>not at all</i> to 7 <i>extremely</i>)
Valid self-report	Self-report with response time between (–5; 15) minutes

to be continued on page 68

TABLE 1. Continued.

C. ESM day measures

Missing self-report	Self-report which was expected but not filled in.
Representativeness ^a	Self-rating on 7-point Likert scale (1 <i>not at all</i> to 7 <i>extremely</i>) of how usual each day was in terms of: <i>mood</i> <i>thoughts</i> <i>activities</i>
Method reactivity ^a	Self-rating on 7-point Likert scale (1 <i>not at all</i> to 7 <i>extremely</i>) of possible effects the sampling might have had on: <i>mood</i> <i>thoughts</i> <i>activities</i>

D. ESM debriefing measures

Disturbance	Subject's response to categorical question (yes/no) on disturbance to the sampling
Difficulties	Subject's response to categorical question (yes/no) on difficulties encountered in filling out the self-report forms
Representativeness ^b	Subject's response to categorical question (yes/no) on how usual the sampling period was in terms of: <i>mood</i> <i>thoughts</i> <i>activities</i>
Method reactivity ^b	Subject's response to categorical question (yes/no) on possible effects the sampling might have had on: <i>mood</i> <i>thoughts</i> <i>activities</i>

^aSee parallel with ESM debriefing measures; ^bSee parallel with ESM day measures.

performed each activity (1 ‘not at all’ to 5 ‘several times a day’) and, if at all, how much they had enjoyed engaging in it (1 ‘not at all’ to 5 ‘very much’).

ESM measures

ESM self-reports collected at each signal consisted of 48 items, of which 36 were Likert scales (see Appendix 2.a for the original Dutch version, and see Appendix 2.b for the English translation). In comparison to the self-reports used in Study 1, two significant modifications were made. First, a general question about momentary QoL (‘In general, how is it going with you right now?’) was added at the beginning of each self-report. This inclusion was required in order to study variability of QoL in daily life and to identify factors that influence momentary QoL. Second, a module on complaints was included to better track potential side effects of treatment. Based on the list of complaints described under ‘Retrospective measures’, the five most frequently associated

with imipramine (Cassano et al., 1994) that were most likely to fluctuate from moment to moment (i.e., headache, dizziness, dry mouth, nausea, and drowsiness) were identified.

Beep level measures. (see Table 1b) Based on the time recorded when the self-report form was completed and the programmed time of the watch, a *valid self-report* was defined as any with a *response time* of minimally -5 to maximally 15 minutes (Delespaul, 1995). The level of *disturbance* generated by the ESM procedure was reported on a 7-point Likert scale at the end of each self-report. At each signal, subjects also rated momentary QoL (*mQoL*, see above), current mood, *physical complaints*, and *enjoyment of activities* on 7-point Likert scales. Mood items were combined into separate scales for positive and negative affective states (*PA*, $\alpha = 0.95$; *NA*, $\alpha = 0.92$, for more details see Chapter 5). Physical complaints included five common side effects of imipramine, mentioned above. Subjects also provided a brief description of their *current activity*, which was later coded into eight categories (i.e., doing nothing, work or study, household chores, shopping, childcare, active leisure, passive leisure, and social activities).

Day level measures. (see Table 1c) Several questions were asked at the end of each sampled day. To assess reasons for *missing self-reports*, subjects were asked to report all times during the day at which they had switched off the watch and the reason for doing so (e.g. personal, social). In addition, subjects were asked to rate on 7-point scales *how usual* (representative) their day had been, and whether the sampling had had any *effects on their mood, thoughts, or activities* during the day.

Debriefing measures. (see Table 1d) At the end of each sampling period a debriefing session was held. Subjects were asked to indicate whether they experienced any *disturbance* from the sampling or whether they encountered any *difficulties* in filling out the self-report forms. Subjects also reported *how representative* their sampled period was in terms of *mood, thoughts, and activities* in daily life, and whether they felt that the sampling had any *effects on their mood, thoughts, and activities*.

Procedure

Following one week with no treatment (*baseline*), patients were randomized to either 50 mg imipramine or placebo. Imipramine was tapered on in the course of a week to 200 mg a day, in a twice-daily dosing regimen, and kept at this dose for the remainder of the study. In case intolerance of the drug occurred, the GP could decrease dose to a minimum of 100 mg a day. Continuing intolerance led to withdrawal from the study. At the end of 6 weeks of treatment, a decision was taken, based upon the judgement of the GP and the wish of the patient, as to further prolongation of double-blind treatment for another 12 weeks (see Figure 1). Patients were scheduled to visit the physicians at regu-

FIGURE 1. ESM sampling periods during Study 2.

lar intervals (Screening, Baseline, and weeks 1, 2, 4, and 6; if treatment was extended, also weeks 10, 14, and 18) for assessment of clinical symptoms (using HDRS and CGI) and potential adverse events.

As in Study 1, patients were sampled for 6 days pre-treatment and 6 days in the 6th week of treatment. In the current study, patients were also asked to fill out ESM forms for 3 days at the end of the first week of double-blind treatment. Furthermore, patients who decided to prolong treatment were sampled for another 6 days in the 18th week of treatment. Questionnaires (QoL VAS, PANAS, complaints, activities, and ESM debriefing) were completed at the end of each sampling period.

Healthy controls were asked to fill out ESM self-report forms for 18 days in total (3 periods of 6 days). The first two periods of 6 days were separated by 6 weeks, and the last sampling period took place 12 weeks after the second sampling period (see Figure 1). Questionnaires were completed, as with the patients, at the end of each ESM period.

Statistical tests

Within-group changes over time were tested with paired *t*-tests or with analysis of variance (ANOVA) with repeated measures. Differences between groups (ESM compliant versus non-compliant patients, depressed versus control subjects) were tested with *t*-tests for two samples, using a Satterthwaite approximation for the degrees of freedom, and χ^2 -tests for the categorical variables. For the relationships between ESM aggregated measures and the conceptually related retrospective measures and the test-retest reliability scores, Pearson correlations were calculated. Cronbach's alpha was calculated as a measure of split-half reliability. All statistical tests were two-tailed. An alpha level of .05 was used.

RESULTS

Feasibility of applying ESM in clinical trials in depression

Although a clinical trial can be designed and set-up in such a way as to fully integrate ESM, the feasibility of using ESM in clinical trials in depression can still be jeopardized by patients not complying with the method.

Compliance

According to the sampling schedule shown in Figure 1, depressed subjects who completed 18 weeks of treatment could have filled in a maximum of 210 ESM self-report forms (beeps), and healthy controls a maximum of 180 beeps. Based on previous experience (Delespaul, 1995), an ESM self-report was considered 'valid' if it was completed in less than 15 minutes after the signal. As subjects can use a different time reference (e.g., a kitchen clock) than the programmed watch to report the time at which the self-report is completed, reports filled in up to 5 minutes before the signal were also considered valid (see also Delespaul, 1995). Of the 83 depressed patients screened, nine subjects had protocol deviations and were excluded from further analyses. Of the 29 control subjects screened, six were found to have had depression (lifetime) or another current psychiatric condition and were therefore excluded from further analyses. The remaining 97 subjects completed 4,145 valid reports in the first sampling period within the acceptable time-window, which is 72% of the maximum possible reports. This percentage is com-

parable to what has previously been found in ESM studies using the same time-window (73% in blue-collar workers, see Csikszentmihalyi and Larson, 1987; e.g., 74% in anxiety disorders, see Dijkman-Caes, 1993).

ESM non-compliant subjects

Prospectively, a minimum of 30 valid beeps (50% of total expected) in the first sampling period was set as a criterion for inclusion in the analysis. Eleven depressed subjects and one control (14.9% versus 4.4% of the participants in the respective groups, $\chi^2 = 1.8$, *ns*) did not meet this requirement. ESM non-compliance in the depressed group was studied in three ways: (1) did non-compliant subjects express more disturbance or difficulties with ESM than compliant subjects? (2) did non-compliant subjects differ from compliant subjects in socio-demographic characteristics?, and (3) were non-compliant subjects more likely to be non-compliant with ESM in subsequent sampling periods than compliant subjects?

At the debriefing, a similar number of compliant and non-compliant subjects reported disturbance from ESM and difficulty in completing the self-reports. Average ratings of disturbance across self-reports were also similar for the two groups.

As noted in Chapter 2, more severe illness may prevent adequate compliance with ESM. The eleven depressed subjects who did not comply adequately with ESM in Study 2 reported greater depressive symptomatology, were younger, and were more likely to be living alone than patients with adequate ESM data (see Chapter 5).

As expected, non-compliant subjects in the first sampling period were more likely than compliant subjects to deliver insufficient ESM data in subsequent sampling periods (of the non-compliant subjects who participated in a second sampling week, 50% remained non-compliant versus 1.7% of compliant subjects; of the non-compliant subjects who participated in a third sampling week, 60% remained non-compliant versus 16.3% of compliant subjects; and all non-compliant subjects who participated in a fourth sampling week remained non-compliant versus 14.3% in the fourth sampling week; all p 's < .05).

In summary, in comparison to subjects with adequate ESM data, non-compliant subjects are more likely to be younger and living alone, to report greater depressive symptomatology, and to be non-compliant in subsequent sampling periods.

Completion rates

Across all sampling periods, 75% of self-reports from compliant subjects were valid (range: 70.1% - 77.9%, see Table 2). About two-thirds of all ESM reports were completed within 5 minutes. Unexpectedly, compared to the imipramine group, the placebo group completed a greater percentage of reports in less than 1 minute in the first sampling period ($t = -2.7$, $df = 61$, $p < .01$) and kept this tendency in subsequent sampling periods (p 's < .16, see Table 2). In spite of randomization, patients in the placebo

TABLE 2. Mean % of valid, out of valid time range, and missing responses for depressed and control groups.

	Cumulative % valid responses within				Out of time range	Missing	Number of programmed reports
	1 min ^a	5 min	10 min	15 min			
<i>Depressed</i>							
Baseline ^b (<i>N</i> = 63)	26.9%	65.5%	75.2%	77.6%	4.1%	18.3%	3790 ^c
Week 1 ^d							
Imi ^e (<i>N</i> =29)	27.1%	66.3%	75.4%	77.5%	5.7%	16.8%	870
Pla ^f (<i>N</i> =30)	38.1%	70.3%	76.3%	77.4%	3.1%	19.4%	900
Week 6 ^b							
Imi (<i>N</i> =23)	28.0%	59.1%	68.0%	71.3%	8.6%	20.1%	1380
Pla (<i>N</i> =26)	39.6%	65.4%	68.9%	70.1%	3.9%	26.0%	1560
Week 18 ^b							
Imi (<i>N</i> =17)	24.2%	56.2%	66.7%	70.2%	8.1%	21.7%	1020
Pla (<i>N</i> =11)	45.8%	70.3%	72.9%	74.4%	5.2%	20.5%	660
<i>Controls</i>							
Baseline ^b (<i>N</i> = 22)	41.3%	74.4%	77.0%	77.9%	3.9%	18.2%	1320
Week 6 ^b (<i>N</i> = 21)	38.3%	70.6%	72.9%	73.5%	6.7%	19.8%	1260
Week 18 ^b (<i>N</i> = 13)	40.5%	72.8%	74.5%	75.6%	8.7%	15.6%	780
TOTAL NUMBERS				10,138	735	2,667	13,540

^aIncluding responses filled in up to 5 minutes before the signal; ^bSampling period of 6 days; ^cOne patient was sampled over 7 days instead of 6; ^dSampling period of 3 days; ^eImi = imipramine; ^fPla = placebo.

group were faster than patients in the imipramine group in completing ESM self-reports even though both groups had equal percentages of valid reports. Completion rates were further investigated by: (1) time of day, (2) day of the week, and (3) day within the sampling period. As there were no significant differences between either groups or sampling periods, all valid beeps were combined in these analyses.

As found with other ESM studies (e.g., Delespaul, 1995), more than two-thirds of the beeps were valid at all diurnal sampling times, except for the first beep (see Figure 2). Significant lower numbers of valid reports were found for the first beep of the day as compared to the other beeps ($F = 45.9, p < .001$). Seventy-four percent of missing first beeps of the day could be related to the fact that subjects were still asleep.

FIGURE 2. Number of valid ESM responses by time of the day. Relationship between beep number and time of the day: 1 = 7:30–9:00 am, 2 = 9:00–10:30 am, 3 = 10:30–12:00 am, 4 = 12:00–1:30 pm, 5 = 1:30–3:00 pm, 6 = 3:00–4:30 pm, 7 = 4:30–6:00 pm, 8 = 6:00–7:30 pm, 9 = 7:30–9:00 pm, 10 = 9:00–10:30 pm.

Analyses done over the days of the week showed that subjects (depressed and controls alike) completed fewer valid responses in the weekend compared to weekdays ($F = 7.7$, $p < .01$) (see Figure 3). In the weekend, more than half of all missing responses could be related to the fact that subjects were asleep. These results are in line with previous ESM studies in anxiety disorders (Dijkman-Caes, 1993) and white-collar workers (van Eck, 1996).

The percentage of valid responses on different research days did not show much variation (see Figure 4). As with other ESM studies (Dijkman-Caes, 1993; Delespaul, 1995; van Eck, 1996), there was no significant decay in response frequencies over the six days sampled ($F = 0.6$, ns).

In summary, 75% of expected reports from compliant subjects were valid. Most missing responses occurred at the beginning of each day (i.e. first beep of the day, between 7:30 and 9:00 a.m.), and in the weekends.

Reasons for missing responses

At the end of the day, subjects could indicate time periods during which the watch was turned off and the reasons. Of the 13,540 programmed beeps, 19.7% (2,667) of the responses were missing. The most common reason was that subjects were still asleep or

FIGURE 3. Number of valid ESM responses by day of the week.

FIGURE 4. Number of valid ESM responses by research day within the sampling week.

had already gone to bed. Other reasons were of social, personal, or technical nature. For 34% of missing responses, no reason was specified.

Method characteristics

Method acceptability

The method acceptability was investigated in the following ways: (1) did depressed patients have more difficulties with ESM self-reports than controls?, (2) did depressed patients express more disturbance from ESM than controls?, (3) did those depressed patients who experienced the highest levels of difficulties, also express the highest levels of disturbance from ESM?, and (4) did depressed subjects who participated in all sampling periods experience less difficulty and disturbance from ESM in the first sampling period than those who did not; in other words, could initial difficulty or disturbance with ESM be a reason for not completing all subsequent sampling periods?

Across all sampling periods, depressed subjects required on average 1 minute more than controls to fill in the self-report form (2.6 ± 2.1 versus 1.6 ± 1.4 , $F = 3.7$, $p = .06$). One would therefore expect depressed patients to express more difficulties in completing the self-report forms than controls. Differences between the two groups were found in the first sampling period only (34.9% of depressed versus 9.1% of controls reported difficulties, $\chi^2 = 5.4$, $p < .05$).

At the end of each ESM report, subjects were asked how much they had been disturbed by the interruption of the beep. Results showed that depressed subjects had a tendency, although not statistically significant, to report more disturbance than healthy controls across all sampling periods (2.5 ± 1.5 versus 1.7 ± 1.0 respectively on a 7-point scale, $F = 2.6$, $p = .11$). However, the numbers of subjects reporting disturbance at the debriefing session were equally distributed across groups for each sampling period (depressed: 58.7%, 47.9%, and 42.9%; controls: 54.5%, 50.0%, and 23.1% for baseline-, 6th-, and 18th-week, respectively). In both depressed and control groups, the number of subjects reporting disturbance decreased over time, but again not significantly ($\chi^2 = 5.0$, $p = .08$).

In the depressed group, the relationship between mean disturbance level and speed of response in the first sampling period was negative, but not statistically significant ($r = -.23$, $N = 63$, $p = .08$). There was no difference in disturbance level in the first sampling period between depressed subjects who had difficulties with ESM and those who did not (2.3 ± 1.1 versus 2.6 ± 1.5 respectively, $t = -.66$, $df = 61$, $p = .51$). Therefore, the higher disturbance levels reported could not be attributed to difficulties with ESM *per se*.

Patients who completed both the 18 weeks of treatment and the four sampling periods did not differ from the other patients in either disturbance levels (2.5 ± 1.4 versus 2.5 ± 1.3 respectively, $t = -.02$, $df = 61$, *ns*) or response time (3.1 ± 2.0 versus 2.4 ± 2.2 respectively, $t = -1.3$, $df = 61$, *ns*) in the first period. During the debriefing session at the

end of the first sampling period, equal numbers of completers and non-completers expressed having difficulties with ESM (32.1% versus 37.1% respectively, $\chi^2 = .17$, *ns*), but non-completers were somewhat more likely to report disturbance from ESM (68.6% versus 46.4% of completers, $\chi^2 = 3.2$, $p = .08$).

In summary, depressed patients expressed more difficulties with ESM than healthy individuals, and took more time to fill in the self-report forms. In addition, depressed patients had a tendency to report slightly greater disturbance from ESM than healthy individuals, which may have been a reason in some individuals – although this was not explicitly mentioned - for not completing all subsequent sampling periods.

Method reactivity

At the end of the day, subjects were asked to rate on 7-point scales the extent to which ESM had any effects on their thoughts, mood, or activities during that day. Thoughts were most likely influenced by the ESM procedure, in both depressed and control groups, with no difference in the extent of reactivity between the two groups (2.4 ± 1.0 versus 1.8 ± 1.0 respectively, $F = 0.1$, *ns*). Depressed and healthy subjects also reported equal influence of ESM with respect to activities (2.2 ± 1.2 versus 1.5 ± 1.0 respectively, $F = 0.5$, *ns*). However, depressed subjects reported more influence on their moods than healthy individuals (2.2 ± 1.2 versus 1.3 ± 0.5 respectively, $F = 4.0$, $p < .05$). Method reactivity was highest in the first sampling period and decreased over time for thoughts ($F = 9.2$, $p < .001$), mood ($F = 4.7$, $p < .01$), and activities ($F = 3.7$, $p < .05$) in both groups (see Table 3).

TABLE 3. ESM reactivity on thoughts, mood, and activities by sampling period as assessed at the end of the day for depressed and control groups combined.

	Thoughts	Mood	Activities
Baseline week	2.6 ± 1.2	2.1 ± 1.3	2.1 ± 1.3
Week 6	1.9 ± 1.1	1.7 ± 1.0	1.8 ± 1.2
Week 18	1.4 ± 0.9	1.4 ± 0.9	1.5 ± 0.8

During the debriefing at the end of the first sampling period, more depressed than healthy subjects reported experimental effects with respect to their moods (39.7% versus 13.6% respectively, $\chi^2 = 5.0$, $p < .05$) and to some extent with respect to their thoughts (63.5% versus 40.9%, $\chi^2 = 3.4$, $p = .06$), but not with respect to their activities (30.2% versus 22.7%, $\chi^2 = 0.4$, *ns*). In subsequent periods, no differences were found between the two groups in experimental effects on moods, thoughts, or activities.

In summary, depressed patients reported greater experimental effects with respect to their moods than healthy individuals. Whether these influences were positive or negative remains unknown, as this was not specifically asked. In general, method reactivity decreased in subsequent sampling periods.

Representativeness

At the end of each day, subjects were asked how 'usual' their day had been on a Likert scale ranging from 1 (not usual) to 7 (very usual). Overall, ESM days were reported to be fairly representative for daily life (mean: 3.8). Across all periods, depressed subjects reported days to be less usual on average than controls ($F = 9.3, p < .01$), but the difference between the two groups diminished over time (as evidenced by a significant Group by Period interaction term; $F = 5.5, p < .01$).

However, subjects were asked during the debriefing session at the end of each sampling week whether they felt the sampled days to be representative with respect to their thoughts, mood, and activities. Here, there were no significant differences between the two groups in the percentage of subjects reporting each sampling period to be representative of their daily lives.

In summary, it is feasible to apply ESM in clinical trials in depression. ESM compliance rates in depression were comparable to rates found in other patient populations and controls. Young patients living alone and with severe depression were most likely non-compliant with ESM and remained non-compliant during subsequent sampling periods. In compliant patients, 75% of self-reports were valid. Because patients were often still asleep, significantly fewer ESM reports were obtained at the beginning of the day and in the weekends. Depressed patients experienced more difficulty with the method, and reported somewhat more disturbance than controls, which might in some cases have discouraged depressed patients from participating in subsequent sampling periods even though 'disturbance from ESM' was never reported as a reason for dropping-out of the study. Depressed patients reported greater method reactivity with respect to moods than healthy individuals and found days to be less usual than healthy individuals. This suggests either, that the patients may not have considered life in the depressed condition as representative, or that patients' ratings are more likely affected by their depressive state.

Utility of ESM for use in clinical trials in depression

The utility of ESM in the context of depression trials depends in the first place on whether the method yields reliable and valid information - as far as this can be investigated - about QoL in daily life of depressed patients and about daily life effects of antidepressant treatment. In the second place, the utility of ESM for depression trials depends

on whether ESM can be shown to be more sensitive - quantitatively or qualitatively - to treatment effects than conventional research methods.

Reliability

Reliability refers to the degree that a test outcome is reproducible under similar conditions. One way of investigating the reliability of ESM is by looking at the stability of measures over time when no systematic change is expected. First, test-retest reliability scores were calculated: (1) by correlating mean levels of ESM measures at baseline and week 6 for controls, and (2) by correlating mean levels of ESM measures at baseline and week 1 for depressed patients, based on the expectation that the clinical state, but not the side effects, during the first week of treatment would have remained unchanged compared to baseline. Secondly, split-half reliability scores were calculated for both groups for the first sampling period. The first half consisted of the uneven sampled days (day numbers 1, 3, and 5), whereas the second half consisted of the even sampled days (day numbers 2, 4, and 6).

Test-retest reliability. Mean levels of mQoL, PA, NA, severity of complaints, and enjoyment of activities were stable over a period of six weeks in healthy individuals (r 's $> .69$, see Table 4). Correlations between mean levels of ESM measures at baseline and the first week of treatment were also high in depressed patients (r 's $> .75$, see Table 4), suggesting that ESM measures are stable over time periods during which no systematic changes in clinical state are expected. As the majority of side effects were expected and also occurred in the first week of treatment, current reliability ratings can be underestimates of the real reliability of the ESM measures.

Split-half reliability. Cronbach's alpha between subjects' means on even sampled days and on uneven sampled days were all above .90, indicating that ESM measures reflect fairly stable individual characteristics (see Table 5).

In summary, on the basis of test-retest and split-half reliability, ESM measures in both depressed patients and healthy controls showed high levels of temporal stability (in mean levels).

Validity

Validity refers to the degree that a test measures what it is intended to measure. As it is subject to the purpose of the use in a specific situation, validity of a test can never be fully demonstrated. However, there are several types of validity (e.g., face validity, construct validity) which may provide for a certain level of confidence in the validity of the test. In this section, a specific form of construct validity (i.e., concurrent validity) is investigated, where ESM measures were expected to correlate positively with conceptually related retrospective measures.

TABLE 4. Test-retest reliability scores in depressed patients (correlation between baseline and week 1) and in controls (correlation between baseline and week 6).

Correlation coefficient for	Depressed (N = 59)	Controls (N = 21)
mQoL	.81***	.74***
PA	.83***	.88***
NA ^a	.88***	.89***
Severity of complaints	.75***	.77***
Enjoyment of activities	.89***	.69***

*** $p < .001$. ^a Number of controls for NA: N = 20.

TABLE 5. Split-half reliability in depressed and healthy individuals on the basis of the first sampling period.

Cronbach's alpha for:	Depressed (N = 63)	Controls (N = 22)
mQoL	.93	.90
PA	.97	.99
NA	.97	.89 ^a
Severity of complaints	.90	.93
Enjoyment of activities	.90	.90

^aN = 21.

TABLE 6. Correlation coefficients between ESM and conceptually related retrospective measures by group on the basis of the first sampling period.

	Depressed (N = 63)	Controls (N = 22)
mQoL	.42***	.58**
PA	.76***	.64***
NA	.64***	.50*
Complaints		
Severity ^a	.30*	.40
Frequency	.71***	.56**
Enjoyment of activities	.65***	.48*

* $p < .05$, ** $p < .01$, *** $p < .001$; ^aDepressed group: N = 59, control group: N = 14.

In both groups, mean levels of ESM measures (mQoL, PA, NA, and enjoyment of activities) were significantly associated with their conceptually related retrospective measures (r 's > .42, p 's < .05, see Table 6). In both groups, a lower association was found between ESM and retrospective measures for severity of complaints than for frequency of complaints (see Table 6).

Sensitivity

Sensitivity is defined, here, as the degree to which a measure can detect differences between two treatment groups. In the context of a clinical trial, the sensitivity of a measure is regarded as an important aspect as it determines, together with the sample size, the chances of finding true treatment differences (see also Chapter 2). The greater the sensitivity and the greater the sample size, the greater the chance of detecting treatment differences. The sensitivity of a measure can be defined as the standardized treatment effect size (STES, also 'standardized difference', see Whitehead, 1992), which is the ratio of the treatment group mean difference Δ to the pooled standard deviation σ . Thus, the smaller the pooled standard deviation, the larger the standardized treatment effect size.

The sensitivity of the sampling strategy in Study 2 was investigated by taking the STES in the 6th week of treatment and addressing the following questions: (1) by what percentage did the current sampling strategy increase STES for ESM measures when compared to one-time measurements, and how did this percentage gain affect the chances of detecting a treatment difference?, (2) what would have been the most efficient sampling strategy to obtain the greatest possible STES for the ESM measures (used as outcome measures) with the smallest number of sampling moments possible?, and (3) how did STES for ESM measures compare with STES for the conceptually related retrospective measures? As similar results were found for all ESM measures (mQoL, PA, NA, severity of complaints, enjoyment of activity), only data on mQoL are shown.

In general, as repeated observations decrease the measurement error, a time sampling strategy is not expected to change the treatment group mean difference Δ , but it is expected to decrease the pooled standard deviation σ of the mean. As a result, STES is expected to increase as a function of the number of observations. In case of m sampled days with n beeps per day, the decrease in variance σ^2 is:

$$g = (1 - (\sigma_S^2 + \sigma_D^2/m + \sigma_B^2/mn) / (\sigma_S^2 + \sigma_D^2 + \sigma_B^2)) \times 100\%$$

where: $(\sigma_S^2 + \sigma_D^2 + \sigma_B^2)$ is the variance of a one-time measurement
 $(\sigma_S^2 + \sigma_D^2/m + \sigma_B^2/mn)$ is the variance of the mean of mn replications
 σ_S^2 is the variation between subjects
 σ_D^2 is the variation between days within a subject

σ_B^2 is the variation between beeps within a day

m is the number of sampled days

n is the number of beeps within a day.

STES for mQoL, considered as a one-time measurement ($m = 1$, $n = 1$), was compared with mQoL as measured throughout the sampling period ($m = 6$, $n = 10$). Results showed that the sampling strategy currently used decreased the variance σ^2 by (g) 26% compared to a one-time measurement of mQoL, which led to an increase in STES of 18% (see Table 7). The larger STES was reflected in a smaller p -value for detecting a difference between the two treatment groups, although in this case neither of the two p -values was significant.

In Study 2, the choice for the number of sampled days (6) and the number of beeps (10) was a pragmatic one, based on previous experiences (Delespaul, 1995). Whether this choice was effective and efficient depends on two factors: (1) Was the maximum STES obtained?, and (2) Was the maximum STES obtained with the smallest number of sampled days and beeps?

In Figure 5, STES is displayed as a function of the number of days (*lines*) and the number of beeps (*X-axis*). As can be seen, STES varied more as a function of the sampled days than as a function of beeps. In general, the greater the number of days and the greater the number of beeps, the greater STES. However, increases of STES occurred as a function of number of days and number of beeps until a certain limit was reached. This limit, the maximum STES (0.332), was determined under the assumption that the number of sampled days m and the number of sampled moments per day n are so large that (σ_D^2/m) and (σ_B^2/mn) can be assumed to be negligible.

The STES found in Study 2 for mQoL (0.328) was at 98.7% of the maximum, so that the current sampling strategy (i.e. 10 times/day for 6 days) was effective in obtaining the highest level of sensitivity for mQoL. In other words, a more intensive sampling regimen would not have led to higher STES. With the aim of obtaining the greatest STES with the fewest sampling moments, the current sampling strategy was not the most efficient. A similar STES for mQoL could also have been obtained with a smaller number of beeps per day (≥ 7), but probably not with a smaller number of sampled days (see Figure 5).

In summary, the sampling strategy used in Study 2 was effective, but not the most efficient, in obtaining the greatest level of sensitivity for mQoL as an outcome measure.

Finally, STES for mQoL was compared with STES for the conceptually related retrospective measure QoL VAS (correlation in the 6th week of treatment for the imipramine group: $r = .69$, $p < .001$, $N = 23$; for the placebo group: $r = .65$, $p < .001$, $N = 26$). To allow comparison of group mean differences and variances of the two measures,

TABLE 7. Observed group mean difference, variance, STES, and related *p*-value for mQoL, one-time measurement versus based on the current sampling strategy (i.e. 10 times a day for 6 days).

	One-time measurement	Current sampling strategy
Δ	0.38	0.38
σ^2	1.78	1.32
STES	0.28	0.33
<i>p</i> -value	0.33	0.26

$\sigma^2 = \sigma_S^2 + \sigma_D^2/m + \sigma_B^2/mn$; STES = $\Delta/\sqrt{\sigma^2}$; *P*-value is based on *t* statistic: $t = \text{STES}/\sqrt{(1/N_1 + 1/N_2)}$ with $N_1 = 23$ (number of subjects in the imipramine group) and $N_2 = 26$ (number of subjects in the placebo group).

TABLE 8. Group mean difference, variance, and STES for mQoL versus QoL VAS, transformed to a scale (−3,3).

	mQoL	QoL VAS
Δ	0.38	0.83
σ^2	1.32	1.79
STES ^a	0.33	0.62
(95%-confidence interval)	(−0.23, 0.89)	(0.06, 1.18)

$\sigma^2 = \sigma_S^2 + \sigma_D^2/m + \sigma_B^2/mn$. STES = $\Delta/\sqrt{\sigma^2}$.

^aAs the imipramine patients differed significantly from placebo patients on the QoL VAS at baseline (39.4 ± 16.1 versus 30.7 ± 15.7 , $t = 2.2$, $df = 61$, $p < .05$) but not in ratings of mQoL (0.2 ± 1.0 versus -0.1 ± 0.9 , $t = 1.2$, $df = 61$, *ns*), we adjusted STES for baseline differences. Again, no difference was found between STES for mQoL (0.10) and STES for QoL VAS (0.23) as the 95%-confidence intervals overlapped: (−0.50, 0.62) versus (−0.47, 0.65) respectively.

FIGURE 5. Standardized treatment effect size for mQoL by number of sampled days and number of sampled beeps. *d* = number of sampled days. * STES for mQoL with sampling strategy used in Study 2 = 0.328. Maximum STES for mQoL = 0.332.

QoL VAS was transformed to a scale ranging from -3 to 3. The transformation was deemed justified as 7-point Likert and visual analogue scales are known to show comparable responsiveness and validity in a randomized trial setting (Jaeschke et al., 1990). Re-scaling the scores for QoL VAS was done as follows:

$$X_r = 3 \times \frac{(X - 50)}{50}$$

where: X_r is the re-scaled QoL VAS score

X is the original QoL VAS score.

Contrary to expectations, STES for mQoL was not significantly greater than STES for QoL VAS, as the 95%-confidence intervals overlapped (see Table 8). Thus, a single ESM item (repeatedly scored) was not found to be more sensitive than a retrospective assessment of a similar item in this study. Although the variance of mQoL was, as expected, smaller than the variance of QoL VAS, the group mean difference for mQoL was, unexpectedly, also smaller.

To summarize the main findings concerning sensitivity, the sampling strategy used in Study 2 (i.e., 10 times a day for 6 days) was effective in attaining the maximum STES for mQoL. It increased STES by 18% over a one-time measurement of mQoL. However, in order to obtain a mQoL measure with the highest level of sensitivity possible, the sampling strategy could have been restricted in the number of beeps per day, to a minimum of 7. Contrary to expectations, mQoL (repeatedly scored) was not found to be more sensitive than a retrospective assessment of a similar item in this study.

DISCUSSION

With the exception of a small number of severely depressed individuals, patients were able to comply with ESM and did so as well as healthy individuals, even though they had more difficulties in completing the self-reports and reported somewhat more disturbance from ESM. In general, those who complied with one sampling period complied equally well with subsequent sampling periods. Over time, initial difficulty and disturbance with ESM in depressed patients subsided, so that the application of ESM to clinical trials can be regarded as feasible and appears promising for long-term clinical trials.

Concurrent validity was high for ESM and the conceptually related retrospective measures for QoL, PA, NA, enjoyment of activities, and frequency of complaints. On the basis of test-retest and split-half reliability analyses, ESM measures were found to be stable over time. By using repeated measurements over the day and across days instead

of one-time measurement, the current sampling strategy (i.e. 10 times a day for 6 days) increased the standardized treatment effect size, thereby increasing the likelihood of detecting true treatment differences. Although the chosen sampling strategy was effective in that it achieved the maximum STES for mQoL, it was not the most efficient choice, as the maximum STES for mQoL could also have been obtained with fewer beeps per day. Another recent application of ESM in a nicotine-patch trial has used a sampling strategy of 8 to 10 beeps a day for 21 days and found differences in nicotine craving and withdrawal symptoms between two different nicotine patches (Shiffman et al., 2000). With only a few experiences to date in applying ESM in clinical trials, it is clear that the design of optimal sampling strategies should be studied more thoroughly, as an objective in itself. Surprisingly, mQoL was not found to be more sensitive than the conceptually related retrospective measure QoL VAS in detecting differences between drug and placebo, in spite of decreasing the error measurement. Comparisons between the two scales on a range from -3 to 3 showed that the group mean difference was greater for QoL VAS than mQoL. Although this outcome is difficult to interpret, two possible explanations are proposed. First, the correlation between the two scales was possibly not sufficient to make such a comparison. In other words, retrospective and moment-to-moment assessments may measure intrinsically different concepts (see discussion of 'subjective happiness' versus 'objective happiness' respectively, in Kahneman, 1999 and see also Chapter 2). Second, in the current debate on the integrity of the double-blind procedure in depression trials due to side effects (Greenberg and Fisher, 1997; Quitkin et al., 2000), some authors suggest that patients report enhanced improvement as a result of experiencing anticipated side effects (Antonuccio et al., 1999). Such a cognitive judgmental process is more likely to affect a retrospective assessment than moment-to-moment reports. It should be said, however, that the comparisons made in terms of the sensitivity of the measures were possibly limited by the choice of the measures used (single-item, self-constructed scales). Future ESM application in depression trials should address the question of whether a relevant ESM index can be developed which is more sensitive in detecting treatment differences than a commonly used primary outcome measure such as HDRS. Interesting as this might be, such an investigation lies beyond the focus of the present research.

As indicated at the beginning of this chapter, the utility of ESM in the context of clinical trials also depends on whether ESM can deliver new insights (not amenable to assessment by other means) into the effects of drug treatments by virtue of measuring prospectively in real-life settings. This objective will be investigated in Chapters 6 & 7. Chapter 5 will first address the differences in daily QoL between depressed and healthy subjects.

REFERENCES

- American Psychiatric Association, 1987. Diagnostic and Statistical Manual of Mental Disorders, Third Edition, revised. American Psychiatric Association, Washington, DC.
- Andrews, F. M., McKennell, A. C., 1980. Measures of self-reported well-being: their affective, cognitive, and other components. *Social Indicators Research* 8, 127-155.
- Antonuccio, D. O., Danton, W. G., DeNelsky, G. Y., Greenberg, R. P., Gordon, J. S., 1999. Raising questions about antidepressants. *Psychother Psychosom* 68(1), 3-14.
- Cassano, G. B., Toni, C., Petracca, A., Deltito, J., Benkert, O., Curtis, G., Hippus, H., Maier, W., Shera, D., Klerman, G., 1994. Adverse effects associated with the short-term treatment of panic disorder with imipramine, alprazolam or placebo. *Eur Neuropsychopharmacol* 4, 47-53.
- Csikszentmihalyi, M., Larson, R., 1987. Validity and reliability of the Experience Sampling Method. *J Nerv Ment Dis* 175(9), 526-537.
- Delepaul, P. A. E. G., 1995. Assessing Schizophrenia in Daily Life: The Experience Sampling Method. Ph.D. dissertation, Maastricht University, Universitaire Pers, Maastricht.
- Dijkman-Caes, C. I. M., 1993. Panic disorder and agoraphobia in daily life. Ph.D. dissertation, Maastricht University, Universitaire Pers, Maastricht.
- Dingemans, P., van Engeland, H., Dijkhuis, J. H., Bleeker, J., 1985. De 'Diagnostic Interview Schedule' (DIS). *Tijdschrift voor Psychiatrie* 27(5), 341-359.
- Greenberg, R. P., Fisher, S., 1997. Mood-mending medicines: probing drug, psychotherapy, and placebo solutions. In: Fisher, S., Greenberg, R. P. (Eds.), *From Placebo to Panacea: Putting Psychiatric Drugs to the Test*. Wiley & Sons, New York, pp. 115-172.
- Guy, W., 1976. ECDEU Assessment Manual for Psychopharmacology. US Department of Health, Education and Welfare, Rockville, MD, pp. 59-70.
- Hamilton, M., 1960. A rating scale for depression. *J Neurol Neurosurg Psychiatr* 23, 56-62.
- Jaeschke, R., Singer, J., Guyatt, G. H., 1990. A comparison of seven-point and visual analogue scales. Data from a randomized trial. *Controlled Clin Trials* 11, 43-51.
- Kahneman, D., 1999. Objective happiness. In: Kahneman, D., Diener, E., Schwarz, N. (Eds.), *Well-being: the foundations of hedonic psychology*. Russell Sage Foundation, New York, pp. 3-25.
- Peeters, F. P. M. L., Ponds, R. W. H. M., Vermeeren, M. T. G., 1996. Affectiviteit en zelfbeoordeling van depressie en angst. *Tijdschrift voor Psychiatrie* 38(3), 240-250.
- Quitkin, F. M., Rabkin, J. G., Gerald, J., Davis, J. M., Klein, D. F., 2000. Validity of clinical trials of antidepressants. *Am J Psychiatry* 157(3), 327-337.
- Shiffman, S., Elash, C. A., Paton, S. M., Gwaltney, C. J., Paty, J. A., Clark, D. B., Liu, K. S., Di Marino, M. E., 2000. Comparative efficacy of 24-hour and 16-hour transdermal nicotine patches for relief of morning craving. *Addiction* 95(8), 1185-1195.
- van Eck, M., 1996. Stress, Mood, and Cortisol Dynamics in Daily Life. Ph.D. dissertation, Maastricht University, Universitaire Pers, Maastricht.
- Watson, D., Clark, L. A., Tellegen, A., 1988. Development and validation of brief measures of positive and negative affect: the PANAS scales. *Journal of Personality and Social Psychology* 54(6), 1063-1070.
- Whitehead, J., 1992. The design and analysis of sequential clinical trials, Second edition. Ellis Horwood Ltd, Chichester, UK.

PART III
MAIN STUDY (STUDY 2)

CHAPTER 5
Quality of life in depression:
Daily life determinants and variability

Barge-Schaapveld, D. Q. C. M., Nicolson, N. A., Berkhof, J., deVries, M. W., 1999.
Quality of life in depression: daily life determinants and variability.
Psychiatry Research 88, 173-189.

Quality of life in depression: Daily life determinants and variability

Identifying daily influences on subjective well-being can be helpful in understanding the burden of depression. This study used experience sampling methodology (ESM) to examine the contribution of mood states, physical complaints, and enjoyment of activities to a momentary measure of quality of life (mQoL), assessed by responses to the question 'In general, how is it going with you right now?'. Sixty-three depressed and 22 healthy control subjects completed ESM self-reports during daily activities, 10 times per day for 6 days. In comparison to control subjects, depressed subjects had lower levels of mQoL, positive mood, and enjoyment of activity, higher negative mood, and more frequent and severe complaints. Depressed subjects were more likely than control subjects to be doing nothing and less likely to be engaged in work. Multilevel regression analysis showed that positive mood and enjoyment of the current activity were associated with higher mQoL, whereas negative mood and complaints were associated with lower mQoL. In depressed subjects, mQoL was more variable over time than in control subjects. In contrast to the ESM results, only negative mood and depression were significant predictors of global measures of QoL. We conclude that QoL has important situational determinants that can in part explain the impact of depression on daily functioning and well-being.

INTRODUCTION

Depressive illness leads to pronounced decrements in the quality of life (QoL), as reflected in subjective well-being and the performance of routine activities and social roles. QoL is a broad construct, encompassing affective, cognitive, behavioral, and physical components (Spilker, 1990). Depression is characterized by disturbances in many or all of these areas, which may explain why QoL is even lower in depression than

in serious somatic disorders like diabetes or arthritis (Wells et al., 1989). Recognition of the burden that depression creates in major life domains has led to increased efforts to assess QoL in clinical research. In addition to clarifying the impact of the illness on patients' lives, QoL instruments provide a way of determining the value of new and existing therapies, beyond their ability to relieve depressive symptoms.

The first studies of QoL in depression employed generic instruments (e.g., Markowitz et al., 1989; Wells et al., 1989). In recent years, new instruments have been developed specifically for use in assessing QoL in depression and other affective disorders (Hunt and McKenna, 1992; Stoker et al., 1992; Endicott et al., 1993; for an overview, see Lehman, 1997). Results indicate that QoL is influenced by affect (Dunbar et al., 1992; Hunt and McKenna, 1992; Corrigan and Buican, 1995), physical symptoms (Markowitz et al., 1989; Endicott et al., 1993; Pyne et al., 1997), and satisfaction with daily activities (Wells et al., 1989; Endicott et al., 1993; Goethe and Fischer, 1995). Clearly, these are influences that will vary from moment to moment throughout the day, reflecting internal states as well as shifting environmental contexts. This means that, in addition to a global lowering of QoL in depression, daily fluctuations in QoL will occur that may be relevant for clinical practice. Because dynamic processes of the sort cannot be studied with existing instruments, new research approaches are needed.

To determine how daily experience contributes to short-term fluctuations in QoL in depressed patients compared to healthy individuals, we used the experience sampling method (ESM). ESM was developed to investigate subjective experience over time and across naturally occurring situations (Csikszentmihalyi and Larson, 1987; deVries, 1992a). Responding to signals at frequent, semi-random intervals, subjects complete brief self-reports concerning their current mental and physical state, activity, location and social context. In the current study, subjects were also asked to evaluate their general well-being at that moment, in response to the question: 'In general, how is it going with you right now?'. We refer to this measure as momentary QoL (mQoL). The prospective nature of ESM assessments offers an advantage over questionnaire measures, which typically summarize experiences over the past week or longer. Retrospective measures are vulnerable to influences of current affective state, forgetting, cognitive re-framing, and other sources of bias (Diener, 1994), which can pose particular problems in depression research (Atkinson et al., 1997). For overviews of previous ESM research on well-being and QoL, with particular reference to mental disorders, see (Barge-Schaapveld et al., 1997) and (deVries et al., 1999).

In the present study, we first use aggregated ESM data to assess the general impact of depression on mQoL, daily mood states, physical complaints, activity patterns, and enjoyment of activities. Results of an earlier study (Barge-Schaapveld et al., 1995) showed that positive affect increased, negative affect decreased, and patterns of time use changed (time spent in chores increased and time spent in passive leisure decreased) following successful treatment of depression. As there was no control group, however, it is

not clear whether these patterns differed, either before or after treatment, from those of healthy individuals.

Next, we develop a multilevel regression model to test the effects of concurrent daily life experiences (negative and positive affect, physical complaints, and enjoyment of activities) on mQoL. There is evidence that these predictors are themselves interrelated; for example, positive correlations have been reported between negative affect and physical complaints (Verbrugge, 1985; Watson, 1988) and between positive affect and enjoyable activities (Watson et al., 1992). The current analysis therefore estimates the relative magnitude of the contribution of each predictor variable, controlling for the others.

Comparing moment-to-moment, day-to-day, and person-to-person variance components of mQoL in the multilevel model can shed new light on the issue of trait versus state aspects of QoL. Traits refer to relatively stable individual differences, whereas states refer to fluctuations within individuals, in response to changing internal conditions and environmental influences. In addition to their widespread usage in psychology, concepts of trait and state have important implications for psychiatric research methodology (Kraemer et al., 1994). Up until now, the few studies that have examined intraindividual fluctuations in QoL in depression have been limited to treatment-related changes (Agosti et al., 1991). A number of studies provide evidence, however, that instability in well-being or in other positive self-evaluations may be more important as markers of vulnerability to depression than low levels of these characteristics *per se*. For example, recent studies indicate that self-esteem is more unstable (Roberts and Kassel, 1997) and labile to the influence of daily events (Butler et al., 1994) in depressed than in non-depressed individuals, and that within-individual variability in measures of well-being is greater in persons with a high risk for depression (Gable and Nezlek, 1998). We therefore expected that mQoL would fluctuate more widely in depressed individuals than in healthy controls. To test this hypothesis, we compare between- and within-person variance estimates obtained separately in the multilevel model for each of the two groups.

Finally, we compare the ESM results to those obtained with more standard questionnaire measures, to determine whether daily life experiences that are relevant to mQoL can also be identified retrospectively. Results of an earlier study of depressed outpatients (Barge-Schaapveld et al., 1995) showed that ESM was capable of revealing subtle changes in daily life experience following clinical improvement that were not identified by a retrospective QoL instrument. Comparison of the results obtained with ESM versus standard questionnaire measures provides a perspective on the unique contributions of a daily life approach to understanding quality of life in depression.

METHODS

Participants

Diagnosis and screening

After the study was approved by a medical ethics committee, subjects were recruited in eight primary care practices in The Netherlands. During a training session, general practitioners (GPs) were given detailed instructions and practice in diagnosing major depressive disorder according to DSM-III-R criteria (American Psychiatric Association, 1987) by means of a semi-structured interview. They also received training in administration of the Hamilton Depression Rating Scale (HDRS, Hamilton, 1960). Research nurses were trained to administer the Diagnostic Interview Schedule (DIS, Dingemans et al., 1985; Robins et al., 1985) to screen control subjects.

Depressed patients

All patients in the study had a primary diagnosis of current major depressive disorder, as assessed by the GPs. The research nurses later obtained DIS diagnoses for descriptive purposes, but these were not used for inclusion or exclusion of patients. To participate in the study, patients had to meet the following criteria: age 18 to 65 years, free of major somatic illness (including abnormal ECG), scoring ≥ 18 on the 17-item version of the HDRS and ≥ 4 on the Clinical Global Impression severity score (CGI, Guy, 1976). Except for the occasional use of temazepam, no current psychotropic medications were allowed. Of the 83 patients screened, five did not meet all of the above criteria (two had HDRS < 18 , one used prohibited psychotropic medication, one had an abnormal ECG, and one was lost to follow-up) and were therefore excluded. Patients received no treatment (pharmacological or other) for depression during the baseline week in which the current data were collected.

Control group

Each individual in The Netherlands is registered as a client of a particular general medical practice. Healthy subjects were recruited from the participating practices to form a control group similar to the patient group in age and sex distribution, employment status, and living circumstances (alone or not). The research nurses administered the DIS to exclude individuals meeting diagnostic criteria for depression (lifetime) or other current psychiatric conditions. Of the 29 control subjects screened, 6 were therefore excluded.

Procedure

During the screening session, study procedures were explained to all subjects and informed consent obtained. The SF-36 Health Survey (SF-36, Ware, 1996), added to the measures after the study began, was completed by a subset of 42 depressed and 18 control subjects. In a separate briefing session, a research nurse explained details of the ESM procedure. Subjects then completed ESM reports for six days, in response to signals from a programmed wristwatch at ten semi-random intervals per day, between 7:30 a.m. and 10:30 p.m. In a final session, the research nurse interviewed subjects as to the representativeness of the sampled days and influences the ESM procedure might have had on daily experiences. Subjects then completed a battery of global, retrospective questionnaires.

Assessments

ESM measures

ESM self-report forms were collated into a booklet for each day. Subjects were instructed to complete all items with reference to the moment at which they received a signal (beep). ESM forms used in the current study are reproduced in (deVries et al., 1999). Measures derived from ESM questionnaires are summarized in the top half of Table 1.

At each beep, subjects rated mQoL, current mood, physical complaints, and enjoyment of activity on 7-point scales. Based on a factor analysis of the 17 mood items, two mood dimensions were identified: positive affect (PA; $\alpha = 0.95$) and negative affect (NA; $\alpha = 0.92$). Subjects also provided a brief description of their *current activity*. Responses were later coded by a trained research assistant. The 57 original codes were collapsed into 8 broader activity categories for the current analysis. Interrater agreement for ESM activity codes is high (van Eck, 1996).

Global measures

Questionnaires completed retrospectively, with reference to the past week, provided global measures of quality of life, mood, physical complaints, enjoyment of daily activities, and depressive symptoms. The measures we used are summarized in the bottom half of Table 1. Subjects were asked to rate the quality of their life on a 100-mm visual analogue scale (Andrews and McKennell, 1980) and to complete the validated Dutch version of the SF-36 (van der Zee et al., 1996). Positive and negative affect were rated by subjects on two 10-item scales (PANAS, Watson et al., 1988). For the five somatic complaints also assessed with ESM (*headache, dizziness, dry mouth, drowsiness, and nausea*), subjects indicated how frequently the complaint had occurred in the previous week (1 *not at all* to 5 *several times a day*) and, if it had occurred, how bothersome it was (1 *not at*

TABLE 1. Description of the measures used.

ESM measures	
mQoL	'In general, how is it going with you right now?' (rated -3 <i>very bad</i> to 3 <i>very good</i>)
PA	Mean of items <i>energetic, cheerful, satisfied, alert, calm, enthusiastic, strong, and happy</i> (rated 1 <i>not at all</i> to 7 <i>extremely</i>)
NA	Mean of items <i>hostile, depressed, tense, lonely, anxious, insecure, guilty, harried, and irritable</i> (rated 1 <i>not at all</i> to 7 <i>extremely</i>)
Complaints	Mean severity for <i>headache, dizziness, dry mouth, drowsiness, and nausea</i> (rated 1 <i>not at all</i> to 7 <i>extremely</i>)
Enjoyment of activity	'How much are you enjoying this activity?' (1 <i>not at all</i> to 7 <i>extremely</i>)
Current activity	Subject's written response coded in eight categories: <i>work or study, household chores, shopping, childcare, social activities (visits and going out), active leisure (e.g., hobbies, sports, taking a walk), passive leisure (e.g., watching TV, reading), or doing nothing</i>
Global measures	
QoL VAS	Rating on 100-mm visual analogue scale (1 <i>worst QoL I can imagine for myself</i> to 100 <i>best QoL I can imagine for myself</i>)
SF-36	Self-rating of global functioning, with two summary scores: MCS = Mental Health Component scale PCS = Physical Health Component scale
PANAS	Self-rating of affect on two dimensions: PA = Positive Affect NA = Negative Affect
Complaints	Average product of the frequency x severity ratings for the five symptoms (see above)
Enjoyment of activities	Average product of the frequency x enjoyment ratings for the eight categories of activity (see above)

all to 5 very). A summary measure was calculated as the average product of the frequency and severity ratings for the five complaints. Finally, for the 15 most common categories of daily activities identified in a previous ESM study of depressed outpatients (Barge-Schaapveld et al., 1995), subjects were asked to report how frequently they had performed each activity in the previous week (1 *not at all* to 5 *several times a day*) and, if performed, how much pleasure they had experienced in that activity (1 *none* to 5 *very much*). As noted above for ESM assessments, we limited the current analysis to eight categories of activity, computing a global measure of enjoyment as the average product of frequency and enjoyment ratings.

Statistical Analysis

Aggregated data

mQoL, PA, NA, and enjoyment of activity scores were averaged across all ESM records for each subject. Severity ratings of physical complaints were averaged for each subject across records for which some level of complaint was reported. Mean severity ratings were then transformed to a scale ranging from 1 *mild* to 6 *severe*. The frequency of physical complaints was defined as the number of times that a subject reported a physical complaint (complaint score ≥ 2), expressed as a percentage of total valid ESM records for that subject. Finally, the time spent in each category of activity was defined as the number of records in which that activity was reported, as a percentage of total valid records.

The significance of differences between depressed and control groups was assessed with two-sample *t*-tests which use a Satterthwaite approximation for the degrees of freedom, and with χ^2 -tests for the categorical variables. Multiple regression and correlation analyses were performed to investigate relationships between global measures and aggregated ESM measures. An alpha level of .05 was used.

Multilevel model

To estimate the effects of mood states, physical complaints, and enjoyment of activities on momentary QoL, we used multilevel or hierarchical linear modelling (Goldstein, 1995; Kreft and de Leeuw, 1998; Sullivan et al., 1999). The hierarchical linear model is a variant of the multiple regression model, appropriate for datasets with a multilevel structure. In our case, three different levels (beep, day, and person) can be distinguished. The response variable (mQoL) is assumed to be related to its determinants by the regression equation:

$$\begin{aligned} \text{mQoL} = & \beta_0 + \beta_1 \times \text{PA} + \beta_2 \times \text{NA} + \beta_3 \times \text{COMPL} + \beta_4 \times \text{ACT} + \beta_5 \times \text{GROUP} + \\ & \beta_6 \times \text{PA} \times \text{GROUP} + \beta_7 \times \text{NA} \times \text{GROUP} + \beta_8 \times \text{COMPL} \times \text{GROUP} + \\ & \beta_9 \times \text{ACT} \times \text{GROUP} + r_D + r_C \end{aligned}$$

The predictors PA, NA, COMPL, and ACT refer to vectors of standardized scores (mean 0, variance 1) for positive affect, negative affect, physical complaints, and enjoyment of activities reported at the beeps. The variable GROUP indicates whether an individual belongs to the depressed or to the control group (dummy coded as 1 or 0, respectively). The β 's are the fixed regression coefficients of the predictors.

Each of the residual vectors r_D and r_C (for depressed and control subjects, respectively) can be decomposed into three terms: a person level random effects vector (r_{3D} or r_{3C}), a day level random effects vector (r_{2D} or r_{2C}), and a beep level residual vector (r_{1D} or r_{1C}). The entries for r_{3D} (or r_{3C}) represent the variability in the mQoL averages per

person that is not explained by the predictors; the entries for r_{2D} (or r_{2C}) represent the variability in the mQoL averages per day within a person that is not explained by the predictors; the entries for r_{1D} (or r_{1C}) represent the residual variability among the mQoL scores of the beeps within a day. The decompositions of r_D and r_C can be represented by the equations:

$$r_D = r_{3D} + r_{2D} + r_{1D} \quad \text{and} \quad r_C = r_{3C} + r_{2C} + r_{1C}$$

The entries of r_{3D} , r_{2D} , and r_{1D} are normally distributed with mean zero and person level variance σ_{3D}^2 , day level variance σ_{2D}^2 , and beep level variance σ_{1D}^2 . Likewise, the entries of r_{3C} , r_{2C} , and r_{1C} are normally distributed with mean zero and person level variance σ_{3C}^2 , day level variance σ_{2C}^2 , and beep level variance σ_{1C}^2 . The different variances express the size of residual variability at the three levels. For instance, if the person variance is large, there is large variability in the mQoL averages per person. As in ordinary linear regression, the variances decrease when additional predictors are included in the model. The entries of r_{1D} (or r_{1C}) are assumed to follow a first-order autoregressive AR (1) process. Disregarding the autocorrelation between consecutive beeps biases the standard errors of the fixed regression coefficients downwards.

Significance of the regression coefficients was tested by dividing the estimated effect by its standard error. This ratio is approximately normally distributed. Tests were two-tailed, even when hypotheses were directional. For testing the significance of the residual variances and the autocorrelation, we used the likelihood ratio test (Bryk and Raudenbush, 1992). We estimated the model parameters (the fixed regression coefficients, the variance components, and the autocorrelation) with the statistical software program MLn (Prosser et al., 1996), which produces maximum likelihood estimates.

RESULTS

Excluded subjects

Four depressed subjects were excluded from the analysis for the following reasons: no data on global questionnaires (2 patients), randomized to double-blind medication during the baseline week (1 patient), and no ratings on mQoL (1 patient). Another reason for exclusion was insufficient ESM data. An ESM self-report was considered valid if it was completed less than 15 minutes after the signal. Eleven depressed subjects and one control (14.9% versus 4.4% of the participants in the respective groups, $\chi^2 = 1.8$, *ns*) completed fewer than 30 valid beeps, the minimum criterion for inclusion in the analysis. These excluded patients were younger (35.5 ± 8.8 years versus 43.4 ± 9.2 years respectively, $t = 2.7$, $df = 14$, $p < .05$) and more likely to be living alone (12.4% versus

TABLE 2. Socio-demographic data for depressed and healthy subjects.

	Depressed N = 63	Controls N = 22
Age (mean ± SD)	43.4 ± 9.2	42.0 ± 11.5
Gender		
male	17 (27.0%)	5 (22.7%)
female	46 (73.0%)	17 (77.3%)
Work status		
working	28 (44.4%)	12 (54.5%)
not working	35 (55.6%)	10 (45.5%)
Living alone		
yes	8 (12.7%)	2 (9.1%)
no	55 (87.3%)	20 (90.9%)
Psychiatric diagnoses (DIS)		
Major Depression Disorder (MDD) only	7 (11.1%)	0 (0.0%)
MDD + other affective disorder	7 (11.1%)	0 (0.0%)
MDD + anxiety disorder	27 (42.9%)	0 (0.0%)
MDD + affective + anxiety disorders	16 (25.4%)	0 (0.0%)
no MDD	6 (9.5%)	22 (100.0%)
Depressive symptoms		
Zung (mean ± SD)*	68.0 ± 10.8	37.3 ± 8.3
Current depressive episode		
first episode	36 (57.1%)	0 (0.0%)
recurrence	27 (42.9%)	0 (0.0%)

* $p < .001$.

6.4%, $\chi^2 = 3.9$, $p < .05$) than patients with adequate ESM data. In addition, patients with inadequate ESM compliance reported greater depressive symptomatology (Zung scale: 73.5 ± 6.2 versus 68.0 ± 10.8 respectively, $t = -2.3$, $df = 19$, $p < .05$). They did not, however, score higher on the HDRS (24.1 ± 4.0 versus 23.8 ± 3.1 , $t = -0.3$, $df = 12$, ns), and the percentage of patients with recurrent major depression did not differ in the two groups (36.4% of the non-compliant versus 57.1% of the compliant patients, $\chi^2 = 1.6$, ns). In the total patient sample, Zung scores were negatively associated with age ($r = -0.27$, $p < .05$), which suggests that the poorer ESM compliance in younger patients may in part reflect their greater illness severity.

Characteristics of patient and control groups

As a result of the procedure for recruiting control subjects (see Methods), there were no differences between the two groups in mean age, sex distribution, living situation (alone or not), or work status (see Table 2). As expected, patients had significantly higher levels

TABLE 3. Descriptive statistics and correlations between ESM aggregated measures.

	Depressed (N = 63)		Controls (N = 22)		<i>t</i>	Pearson <i>r</i> (N = 85)			
	Mean	SD	Mean	SD		2.	3.	4.	5.
1. mQoL	0.08	0.92	2.07	0.47	9.7***	0.77**	-0.76**	-0.60**	0.61**
2. PA	2.23	1.08	4.67	1.21	8.8***	-	-0.54**	-0.43**	0.69**
3. NA	2.29	0.98	1.08	0.11	-5.7***	-	-	0.47**	-0.43**
4. Complaints	1.87	0.71	1.11	0.16	-5.0***	-	-	-	-0.47**
5. Enjoyment of activity	4.20	0.96	5.26	0.68	4.8***	-	-	-	-

* $p < .05$. ** $p < .01$. *** $p < .001$, two-tailed.

of depressive symptoms than controls (Zung scale: $t = 13.8$, $df = 48$, $p < .001$). For 36 (57.1%) of the patients, the current major depressive episode was a first occurrence. DIS results indicated that the majority of the patients (54 out of 63) had a secondary, comorbid psychiatric disorder; as shown in Table 2, 68% of the depressed patients also met criteria for an anxiety disorder. Although all patients were diagnosed by trained physicians as meeting DSM III-R criteria for current major depression, six patients did not meet these criteria as assessed with the DIS; an earlier report has shown, however, that the DIS may underdiagnose major depression in community samples (Helzer et al., 1985). With one exception (obsessive compulsive disorder, never treated) on the basis of DIS results, control subjects were free of current psychiatric disorder and had no lifetime history of depressive disorder.

QoL in daily life

ESM compliance

The 85 subjects (63 patients and 22 controls) completed a total of 3966 valid reports (77.8% of the maximum possible), with no difference in the average number of valid ESM reports completed by subjects in either group (depressed: 46.6 ± 7.4 reports; controls: 46.7 ± 7.9 reports; $t = -0.1$, $df = 35$, *ns*). However, depressed subjects took longer on average to complete a report (2.7 ± 2.1 minutes vs. 1.6 ± 1.4 minutes for controls, $t = 2.7$, $df = 56$, $p < .01$).

Aggregated ESM measures

As expected, depressed individuals experienced lower average levels of mQoL than control subjects (see Table 3). These levels of mQoL were negatively associated to Zung scores in both groups, but only significant in the depressed group ($r = -0.59$, $p < .01$ versus $r = -0.32$, *ns* in controls). No other socio-demographic characteristic stated in

FIGURE 1. Frequency and severity of each type of physical complaint. a = dry mouth; b = drowsiness; c = headache; d = nausea; e = dizziness. X-axis: Frequency of ESM reports mentioning each complaint, expressed as a percentage of total valid reports, was first calculated for each subject. The length of a bar represents the mean frequency of that complaint over all subjects in each group. Depressed: $N = 63$; controls: $N = 22$. Y-axis: A mean severity rating was first calculated for each subject's physical complaints, including only those ESM reports in which the specific complaint was recorded. Placement of the bars indicates the mean severity rating for each complaint in the subset of subjects who reported that complaint. Depressed: ^a $N = 48$, ^b $N = 54$, ^c $N = 57$, ^d $N = 45$, ^e $N = 51$; controls: ^a $N = 6$, ^b $N = 8$, ^c $N = 14$, ^d $N = 3$, ^e $N = 1$.

Table 2 (i.e. age, gender, work status, living circumstances, current depressive episode) was significantly associated with mQoL either in the control or the depressed groups. Furthermore, patients reported higher NA, lower PA, more physical complaints, and less enjoyment of the current activity. Overall, correlations between the measures were statistically significant and in the expected direction. When calculated separately, similar correlational patterns (not shown) were found in both groups.

Figure 1 shows average frequency of ESM complaint reports (x-axis), and mean severity ratings for physical complaints for subjects who reported a particular complaint (y-axis) in the two groups. Over all ESM reports, each of the five physical complaints was reported by more than 70% of the depressed subjects. In contrast, complaints were rare in the control group: significantly fewer control subjects than patients ever experienced dizziness ($\chi^2 = 40.1$), nausea ($\chi^2 = 22.2$), dry mouth ($\chi^2 = 16.8$), or drowsiness ($\chi^2 = 20.1$; all p 's < .001). Headache was relatively common in the control group, but still occurred in significantly fewer subjects than in the depressed group ($\chi^2 = 8.5$, $p < .01$). Each complaint occurred with a greater frequency throughout the ESM sampling period in depressed than in control subjects (headache: $t = -4.1$, $df = 42$; dizziness: $t = -6.8$, $df = 63$; dry mouth: $t = -6.7$, $df = 71$; nausea: $t = -4.9$, $df = 77$; drowsiness:

FIGURE 2. Frequency and enjoyment of each category of activity. a = active leisure; b = child care; c = passive leisure; d = social activities; e = doing nothing; f = work or study; g = chores; h = shopping. X-axis: Frequency of ESM reports mentioning each activity, expressed as a percentage of total valid reports, was first calculated for each subject. Length of the bars represents the mean frequency over all subjects in each group. Depressed: $N = 63$; controls: $N = 22$. Y-axis: A mean enjoyment rating was first calculated for each subject's activities, including only those ESM reports in which the specific activity was recorded. Placement of the bars indicates the mean enjoyment rating for each activity in the subset of subjects who reported that activity. Depressed: ^a $N = 38$, ^b $N = 22$, ^c $N = 63$, ^d $N = 43$, ^e $N = 48$, ^f $N = 14$, ^g $N = 62$, ^h $N = 35$; controls: ^a $N = 17$, ^b $N = 12$, ^c $N = 9$, ^d $N = 22$, ^e $N = 10$, ^f $N = 11$, ^g $N = 12$, ^h $N = 22$.

$t = -8.7$, $df = 82$; all p 's $< .001$). Complaints were also rated as more severe in the depressed than in the control group, with statistically significant differences observed for drowsiness ($t = -3.1$, $df = 13$, $p < .01$), headache ($t = -2.8$, $df = 47$, $p < .01$), and nausea ($t = -3.7$, $df = 5$, $p < .05$).

With regard to reported activities, more depressed than control subjects reported at times to be doing nothing ($\chi^2 = 7.9$, $p < .01$) and fewer depressed patients engaged in work activities ($\chi^2 = 8.0$, $p < .01$), even though the two groups did not differ in employment status. As shown in Figure 2, there were few differences between the two groups in the frequency of performing various activities. Depressed subjects spent a greater percentage of time in doing nothing than controls ($t = -4.7$, $df = 77$, $p < .001$). In contrast to the small differences in time use, the groups differed markedly in the level of enjoyment experienced in daily activities, with depressed individuals reporting significantly less enjoyment than controls in all activities (doing nothing: $t = 3.6$, $df = 22$; work, study: $t = 3.2$, $df = 24$; chores: $t = 3.7$, $df = 38$; shopping: $t = 3.8$, $df = 36$; passive leisure: $t = 4.6$, $df = 60$; social activities: $t = 3.9$, $df = 46$; all p 's $< .01$), except child care ($t = 1.6$, $df = 15$, ns) and active leisure ($t = 1.3$, $df = 22$, ns).

TABLE 4. Multilevel model estimates for momentary QoL (mQoL).

Variable	<i>B</i>	SE <i>B</i>	<i>Z</i> ^b
<i>(a) Main effects model</i>			
Intercept	.76	.09	8.5****
Beep level			
PA	.56	.03	17.4****
NA	-.47	.03	-18.9****
Complaints	-.34	.02	-15.3****
Enjoyment of activity	.05	.01	3.9***
Person level			
Group ^a	.29	.12	2.5*
<i>(b) Full model with interaction terms</i>			
Beep level by person level			
PA x Group	-.02	.07	-.27
NA x Group	-.19	.10	-1.85
Complaints x Group	.25	.09	2.92**
Enjoyment of activity x Group	-.00	.03	-.04

^a Depressed = 1; Control = 0; ^b *Z*-values are calculated by dividing the estimated regression coefficient; (*B*) by its standard error (SE *B*) (Bryk and Raudenbush, 1992); * *p* < .05. ** *p* < .01. *** *p* < .001. **** *p* < .0001, two-tailed; *Note.* The analysis is based on 3966 ESM reports. For the full model, autocorrelations between successive mQoL observations were estimated as 0.400 in the depressed group and 0.272 in the control group, both *p*'s < .0001, likelihood ratio test.

TABLE 5. Explained variance in mQoL at each level of the multilevel model.

	% Explained variance ^a	
	Main effects model	Full model
Depressed group		
Person level	63.1	63.2
Day level	51.1	51.1
Beep level	41.2	41.2
Control group		
Person level	38.9	34.3
Day level	42.8	46.9
Beep level	26.7	27.3

^a Change in residual variances after addition of predictors, expressed as a percentage of the baseline model estimates.

Daily life influences on mQoL

We performed multilevel regression analysis to clarify the contribution of daily life experiences to the overall decrement in mQoL in depression. The first model estimated the main effects of predictor variables, prior to the addition of interaction terms. As shown in Table 4a, all four beep level variables had significant main effects on mQoL. Positive mood states and enjoyment of the current activity were clearly associated with a higher mQoL, whereas negative mood states and physical complaints were associated with lower mQoL. The small but significant effect of the person level variable Group confirms that mQoL levels were lower on average in the depressed group. Notably, when the beep level predictors PA, NA, complaints, and enjoyment of current activity were removed from the model, Group had a much larger effect ($B = -1.9$, $Z = -12.7$, $p < .0001$), which indicates that the effect of a major depression on mQoL was largely mediated by these other variables.

Interaction terms were next added to the model to test for differences between depressed and control groups in the importance of the beep level predictors. All main effects that were found in the first model (Table 4a) remained significant. Table 4b therefore presents only results for the interaction terms in the full model. Physical complaints had a significantly less negative effect on mQoL in the depressed than in the control group. NA, on the other hand, tended to have a more negative influence on mQoL in the depressed group ($p < .10$).

The strength of these findings can be evaluated by examining how much of the variance in mQoL is explained by each model (i.e., the main effects model and the full model with interaction effects). As independent variables are added to a model with only the fixed effect of Group (which we will refer to as the baseline model), the residual mQoL variances observed at each level in the model decrease; these changes in variance components can be used to estimate the percentage of baseline variance in mQoL that is explained, at each level, by the chosen set of predictor variables (for further details, see Kreft and de Leeuw, 1998). In Table 5, explained variances are shown, expressed as percentages of baseline variances. In the main effects model, beep and person level variables together accounted for a considerable percentage of the variability in mQoL at all three levels in the control group, with an even better fit in the depressed group. It is clear that the addition of interaction terms (full model) did little to improve the model, as the percentages of overall explained variance did not increase. For this reason, the group by complaint effect (see Table 4), although significant, should be interpreted with caution.

Variability in mQoL

To test the hypothesis that mQoL would show greater variability in depressed than in control subjects, we estimated the variances of the baseline model as shown in Table 6. As predicted, mQoL was less stable within depressed than within control subjects. Beep level variance was significantly larger in the depressed group (likelihood ratio test, $p <$

TABLE 6. mQoL variance components in the multilevel reference model.

Variance estimate	
Depressed group	
Person level	.76
Day level	.18
Beep level	.71
TOTAL	1.65
Control group	
Person level	.18
Day level	.15
Beep level	.33
TOTAL	.66

Note. All variance estimates are statistically significant, $p < .0001$, likelihood ratio test (Bryk and Raudenbush, 1992).

.00001). In addition, the significant ($p < .05$) difference between the two groups in person level variance indicates greater heterogeneity in average mQoL levels among subjects in the depressed group. Differences between depressed and control groups in day level variability, on the other hand, were not significant.

Examining the contributions of person, day, and beep level variance components to total variance provides information about the relative importance of intraindividual ('state') versus interindividual ('trait') variability in mQoL. Based on the data in Table 6, person level variance in the depressed group represented 46% of the total variance; day level, 11%; and beep level, 43%. In the control group, the distribution of variance components was 27% at the person level, 23% at the day level, and 50% at the beep level. Thus, there was substantial intraindividual (beep level and day level) as well as interindividual (person level) variability in mQoL in both groups. Beep level variance was larger than day level variance, indicating that mQoL fluctuated more widely within than between days.

Predictors of global QoL

How do the ESM findings correspond to global assessments made at the end of the week? First, we examined the correlations between each of the ESM aggregated measures (mQoL, PA, NA, complaints and enjoyment of activities) and its related global assessment. All correlation coefficients were statistically significant ($r \geq 0.70$, all p 's $< .01$, one-tailed), except for the correlation between mean mQoL (aggregated per subject) and SF-36 PCS ($r = 0.12$, ns ; one-tailed). Similar patterns were found in both

TABLE 7. Summary of regression analysis for global measures predicting QoL VAS and SF-36 MCS scores ($N = 85$).

Variables	QoL VAS			SF-36 MCS		
	<i>B</i>	SE <i>B</i>	β	<i>B</i>	SE <i>B</i>	β
Global measures						
PA	.36	.25	.14	.28	.15	.18
NA	-.68	.22	-.27**	-.41	.14	-.27**
Complaints	-.36	.46	-.06	-.27	.27	-.08
Enjoyment of activity	1.03	.73	.13	.27	.46	.06
Group ^a	-21.70	5.19	-.39****	-14.59	3.15	-.45****

^a Depressed = 1; Control = 0; * $p < .05$. ** $p < .01$. *** $p < .001$. **** $p < .0001$, two-tailed; Note. Independent variables were entered simultaneously. $R^2 = .68$ ($F = 33.0$, $p < .0001$) for the equation predicting QoL VAS; $R^2 = .79$ ($F = 39.3$, $p < .0001$) for SF-36 MCS.

groups, except for the correlation between mean mQoL and SF-36 MCS, which was positive in the depressed group only (depressed: $r = 0.29$, $p < .05$; controls: $r = -0.12$, $n.s.$; one-tailed).

Next, multiple regression analyses were conducted with the global assessments QoL VAS and SF-36 MCS as dependent variables and retrospective measures of PA, NA, complaints, and enjoyment of activities as independent variables. Results are shown in Table 7. In contrast to the multilevel results for ESM measures, although depression (the variable Group) was again a good predictor of QoL measures, only NA had a significant added effect.

DISCUSSION

This study used experience sampling methodology (ESM) to investigate two aspects of the quality of life in depression: subjective well-being and daily functioning. Well-being, or momentary QoL (mQoL), was assessed with the question 'In general, how is it going with you right now?'. As expected, depressed subjects experienced lower levels of mQoL than healthy controls. Results of multilevel regression analysis indicated that positive affect, negative affect, and physical complaints had large independent effects on mQoL, with enjoyment of activities making a small but significant additional contribution. Although depression had a major effect on mQoL when it was the only predictor, its estimated effect decreased markedly after the addition of the daily experience variables to the model. In other words, these variables partially mediated the effect of depression on mQoL. On the other hand, the finding that depression continued to have a significant effect on mQoL after controlling for mood, physical complaints, and enjoyment of activities means that other, unmeasured aspects of depression

had an impact on self-assessed well-being. These could include, for example, cognitive disturbances, negative social interactions, or difficulty in coping with daily stressors. Finally, it is important to note that the same variables were predictors of mQoL in healthy control subjects as in depressed subjects. The total percentage of mQoL variance explained was clearly less in the control than in the depressed group, however. We speculate that environmental contexts (social and work activities, for example) may have had larger influences on mQoL in healthy individuals, and that these effects were not mediated by the predictor variables in our model.

Depressed subjects were much more likely to report frequent and/or severe physical complaints than control subjects were. Because the complaints we assessed (dry mouth, dizziness, drowsiness, nausea, and headache) are considered to be common side effects of antidepressants (Cassano et al., 1994), it was surprising to find that the majority of patients experienced these symptoms prior to any treatment. A recent study of untreated depressed patients in primary care, however, confirms that symptoms resembling side effects are very common (Rollman et al., 1997). The fact that negative mood states can trigger physical symptoms (Verbrugge, 1985) may provide some explanation. Although aggregated ESM measures of NA and complaints were indeed positively correlated, both variables made independent contributions to mQoL in the current model.

Variance component estimates in the multilevel model confirmed the importance of both trait and state aspects of mQoL. The finding that more than half of the total variance represented intraindividual fluctuations (beep and day level) points to a large influence of transient situational factors on mQoL in both groups. As hypothesized, depressed subjects showed greater within-person variability in mQoL, from moment to moment and from day to day, than controls. This instability in subjective well-being could be a temporary phenomenon, related to a depression-induced dysregulation of normal oscillations in mood (see, for example, Hall et al., 1991), or it could be related to a pre-existing trait (like neuroticism, Eid and Diener, 1999) associated with greater vulnerability to negative daily experiences (Gable and Nezlek, 1998). This remains an important question for future longitudinal studies. Interindividual variability was also greater in the depressed than in the control group; we speculated that differences in mQoL levels among depressed patients might correlate with symptom severity (Zung score), which they did ($r = -0.59, p < .001$). This was not the case in the control group ($r = -0.32, ns$). We found no association, however, between within-subject variability in mQoL and Zung scores in either the depressed group ($r = 0.05, ns$) or in the controls ($r = 0.18, ns$).

A second aspect of QoL, daily functioning, was operationalized as the frequency with which an individual engaged in productive, social, and leisure activities, in contrast to inactivity, over the six days of experience sampling. Analysis of time use patterns showed that fewer depressed individuals reported work or study activities. In addition, a greater proportion of the depressed group reported daily periods of 'doing nothing',

and this activity state represented a greater percentage of the daily time budget for depressed than for control subjects. Previous research on QoL in depression has mentioned reductions in productive, social or leisure activities (for a recent review, see Katschnig and Angermeyer, 1997). We, however, found no significant differences between depressed and control groups in time spent in social, leisure, or maintenance activities. An earlier ESM study of time use in psychiatric and psychosomatic disorders and healthy controls showed that percentages of time spent doing nothing was higher in severe psychiatric disorders (including major depression); furthermore, doing nothing was associated with low PA and high NA, suggesting that this state may be a behavioral marker of low QoL (Barge-Schaapveld et al., 1997). Due to the poor reliability of retrospective estimates of time use (Bernard et al., 1984), time-sampling methods like ESM may be especially valuable in assessing illness-related reductions in productive and enjoyable activities. Although it may be impossible to unravel the causal connection between activities and psychopathological symptoms, case studies provide some evidence that therapeutic attempts to influence patterns of time use can be effective in improving mental status (Delle Fave and Massimini, 1992; Barge-Schaapveld et al., 1997).

Ratings of mQoL averaged over the sampling period were highly correlated with global assessments of QoL. Whereas ESM measures of NA, PA, physical complaints, and enjoyment of activities were highly associated with mQoL, however, only NA was a significant predictor of global QoL in a regression analysis using aggregated or questionnaire measures of the same variables. The greater sensitivity of mQoL to transient states and daily experiences underscores the potential value of the ESM approach as a tool in understanding changes in QoL during the course of depression and its treatment.

Whether an ESM approach to QoL assessment is 'better' than validated questionnaire or interview measures, however, will depend on the research questions, the setting, and the resources. A drawback of ESM is that it is relatively time-consuming for both the participant and the researcher. The demands of repeatedly completing ESM forms over several days may prove too great for some depressed patients, especially individuals with limited education, cognitive disturbances, or the elderly (Kraan et al., 1992; Wilson et al., 1992). To the extent that these factors result in refusal to participate or drop-outs during ESM, they could bias results. Whereas drop-outs in the current study were not significantly more common among patients than controls, the finding that patients who did not adequately complete the ESM study had higher Zung scores and were somewhat younger than patients included in the analysis does suggest that the sample may not have been completely representative of the population of depressed patients in primary care settings. However, the ability of the majority of the participants to complete the study, as well as successful previous applications of ESM in psychiatric disorders (deVries, 1992a; Barge-Schaapveld et al., 1995; Delespaul, 1995), shows that the method is feasible in major depression.

Beyond research applications, ESM has potential for use in clinical practice. Individualized profiles of quantitative ESM results and qualitative information obtained during the debriefing session can, in our experience, provide patients and therapists with valuable insights (deVries, 1992b; Donner, 1992). Individual therapies could be tailored to promote situations or states associated with maximum mQoL and to reduce exposure to or improve coping with situations that have negative effects on mQoL. ESM could also be adapted for monitoring treatment adherence, or performance and response to homework assignments in cognitive or behavioral interventions (Donner, 1992). Future studies are needed to supplement descriptive case studies, which are currently the only source of information about clinical applications of ESM in psychiatric disorders.

The study had a number of limitations. Firstly, we assessed momentary quality of life with a single item (mQoL), which has psychometric disadvantages compared to multi-item measures (see Diener, 1984). In favor of the measure, the strong correlations between average mQoL scores and the mental component of the SF-36, a widely accepted multi-item measure, support the construct validity of mQoL, and the frequently repeated measurements of mQoL can also be expected to increase the reliability of the results (Kraemer et al., 1994). More work is needed, however, to develop a valid and reliable multi-item mQoL scale. Secondly, several variables that are likely to have important influences on QoL were not examined; these include daily events (Emmons, 1991) and the quality of social interactions (Gannon et al., 1992), trait characteristics such as neuroticism (McCrae and Costa, 1991), and long-term influences, such as life satisfaction (Barry, 1997) or the quality of the living environment (e.g., employment, housing, social networks) (Katschnig and Angermeyer, 1997). Finally, interpretation of the state versus trait aspects of mQoL is limited by the short time-frame (six days) of the study. Longitudinal follow-up through treatment and clinical recovery, using the same measures, will be necessary to determine whether decreased mQoL levels and increased lability of mQoL are state characteristics of current depression or whether residual symptoms or 'scars' remaining after a depressive episode result in persistent, traitlike changes in mQoL and its components. Similarly, follow-up data are needed to assess whether ESM measures can help predict short-term compliance with treatment, early response to treatment, or longer-term clinical outcome.

REFERENCES

- Agosti, V., Stewart, J. W., Quirk, F. M., 1991. Life satisfaction and psychosocial functioning in chronic depression: effect of acute treatment with antidepressants. *Journal of Affective Disorders* 23(1), 35-41.
- American Psychiatric Association, 1987. *Diagnostic and Statistical Manual of Mental Disorders*, 3rd ed. revised. American Psychiatric Association, Washington, DC.

- Andrews, F. M., McKennell, A. C., 1980. Measures of self-reported well-being: their affective, cognitive, and other components. *Social Indicators Research* 8, 127-155.
- Atkinson, M., Zibin, S., Chuang, H., 1997. Characterizing quality of life among patients with chronic mental illness: a critical examination of the self-report methodology. *American Journal of Psychiatry* 154(1), 99-105.
- Barge-Schaapveld, D. Q. C. M., Nicolson, N. A., Delespaul, P. A. E. G., deVries, M. W., 1997. Assessing daily quality of life with the Experience Sampling Method. In: Katschnig, H., Freeman, H., Sartorius, N. (Eds.), *Quality of Life in Mental Disorders*. John Wiley & Sons Ltd, Chichester, pp. 95-107.
- Barge-Schaapveld, D. Q. C. M., Nicolson, N. A., Gerritsen van der Hoop, R., deVries, M. W., 1995. Changes in daily life experience associated with clinical improvement in depression. *Journal of Affective Disorders* 34, 139-154.
- Barry, M. M., 1997. Well-being and life satisfaction as components of quality of life in mental disorders. In: Katschnig, H., Freeman, H., Sartorius, N. (Eds.), *Quality of Life in Mental Disorders*. John Wiley & Sons, Chichester, pp. 31-42.
- Bernard, H. R., Killworth, P., Kronenfeld, D., Sailer, L., 1984. The problem of informant accuracy: the validity of retrospective data. *Annual Review of Anthropology* 13, 495-517.
- Bryk, A. S., Raudenbush, S. W., 1992. *Hierarchical Linear Models: Applications and Data Analysis Methods*. Sage Publications, London.
- Butler, A. C., Hokanson, J. E., Flynn, H. A., 1994. A comparison of self-esteem lability and low trait self-esteem as vulnerability factors for depression. *Journal of Personality and Social Psychology* 66, 166-177.
- Cassano, G. B., Toni, C., Petracca, A., Deltito, J., Benkert, O., Curtis, G., Hippus, H., Maier, W., Shera, D., Klerman, G., 1994. Adverse effects associated with the short-term treatment of panic disorder with imipramine, alprazolam or placebo. *European Neuropsychopharmacology* 4, 47-53.
- Corrigan, P. W., Buican, B., 1995. The construct validity of subjective quality of life for the severely mentally ill. *Journal of Nervous and Mental Disease* 183, 281-285.
- Csikszentmihalyi, M., Larson, R., 1987. Validity and reliability of the Experience Sampling Method. *Journal of Nervous and Mental Disease* 175(9), 526-537.
- Delespaul, P. A. E. G., 1995. *Assessing Schizophrenia in Daily Life: The Experience Sampling Method*. Ph.D. dissertation, Maastricht University, Universitaire Pers, Maastricht.
- Delle Fave, A., Massimini, F., 1992. The ESM and the measurement of clinical change: a case of anxiety disorder. In: deVries, M. W. (Ed.), *The Experience of Psychopathology: Investigating Mental Disorders in Their Natural Settings*. Cambridge University Press, Cambridge, pp. 280-289.
- deVries, M. W., 1992a. *The Experience of Psychopathology: Investigating Mental Disorders in Their Natural Settings*. Cambridge University Press, Cambridge.
- deVries, M. W., 1992b. The uses of the ESM in psychotherapy. In: deVries, M. W. (Ed.), *The Experience of Psychopathology: Investigating Mental Disorders in Their Natural Settings*. Cambridge University Press, Cambridge, pp. 255-259.
- deVries, M. W., Delespaul, P. A. E. G., Nicolson, N. A., 1999. Experience Sampling Method (ESM). In: Salek, S. (Ed.), *Compendium of Quality of Life Instruments*. John Wiley & Sons, Chichester, pp. 2L:6; 2L:6a.
- Diener, E., 1984. Subjective well-being. *Psychological Bulletin* 95(3), 542-575.
- Diener, E., 1994. Assessing subjective well-being: progress and opportunities. *Social Indicators Research* 31, 103-157.
- Dingemans, P., van Engeland, H., Dijkhuis, J. H., Bleeker, J., 1985. De 'Diagnostic Interview Schedule' (DIS). *Tijdschrift voor Psychiatrie* 27(5), 341-359.
- Donner, E., 1992. Expanding the experiential parameters of cognitive therapy. In: deVries, M. (Ed.), *The Experience of Psychopathology: Investigating Mental Disorders in Their Natural Settings*. Cambridge University Press, Cambridge, pp. 260-269.

- Dunbar, G. C., Stoker, M. J., Hodges, T. C. P., Beaumont, G., 1992. The development of SBQOL: a unique scale for measuring quality of life. *British Journal of Medical Economics* 2, 65-74.
- Eid, M., Diener, E., 1999. Intraindividual variability in affect: reliability, validity, and personality correlates. *Journal of Personality and Social Psychology* 76, 662-676.
- Emmons, R. A., 1991. Personal strivings, daily life events, and psychological and physical well-being. *Journal of Personality* 59(3), 453-472.
- Endicott, J., Nee, J., Harrison, W., Blumenthal, R., 1993. Quality of Life Enjoyment and Satisfaction Questionnaire: a new measure. *Psychopharmacology Bulletin* 29(2), 321-326.
- Gable, S. L., Nezlek, J. B., 1998. Level and instability of day-to-day psychological well-being and risk for depression. *Journal of Personality and Social Psychology* 74(1), 129-138.
- Gannon, L., Vaux, A., Rhodes, K., Luchetta, T., 1992. A two-domain model of well-being: everyday events, social support, and gender-related personality factors. *Journal of Research in Personality* 26(3), 288-301.
- Goethe, J. W., Fischer, E. H., 1995. Functional impairment in depressed inpatients. *Journal of Affective Disorders* 33, 23-29.
- Goldstein, H., 1995. *Multilevel Statistical Models*, 2nd ed. Arnold, London.
- Guy, W., 1976. *ECDEU Assessment Manual for Psychopharmacology*. US Department of Health, Education and Welfare, Rockville, MD, pp. 59-70.
- Hall, D. P., Jr., Sing, H. C., Romanoski, A. J., 1991. Identification and characterization of greater mood variance in depression. *American Journal of Psychiatry* 148, 1341-1345.
- Hamilton, M., 1960. A rating scale for depression. *J Neurol Neurosurg Psychiat* 23, 56-62.
- Helzer, J. E., Robins, L. N., McEvoy, L. T., Spitznagel, E. L., Stoltzman, R. K., Farmer, A., Brockington, I. F., 1985. A comparison of clinical and diagnostic interview schedule diagnoses. *Archives of General Psychiatry* 42, 657-666.
- Hunt, S. M., McKenna, S. P., 1992. The QLDS: A scale for the measurement of quality of life in depression. *Health Policy* 22, 307-319.
- Katschnig, H., Angermeyer, M. C., 1997. Quality of life in depression. In: Katschnig, H., Freeman, H., Sartorius, N. (Eds.), *Quality of Life in Mental Disorders*. John Wiley & Sons Ltd, Chichester, pp. 137-147.
- Kraan, H., Meertens, H., Hilwig, M., Volovics, L., Dijkman-Caes, C. I. M., Portegijs, P., 1992. Selecting measures, diagnostic validity and scaling in the study of depression. In: deVries, M. W. (Ed.), *The Experience of Psychopathology: Investigating Mental Disorders in Their Natural Settings*. Cambridge University Press, Cambridge, pp. 324-338.
- Kraemer, H. C., Gullion, C. M., Rush, A. J., Frank, E., Kupfer, D. J., 1994. Can state and trait variables be disentangled? A methodological framework for psychiatric disorders. *Psychiatry Research* 52, 55-69.
- Kreft, I., de Leeuw, J., 1998. *Introducing Multilevel Modeling*. Sage Publications, London.
- Lehman, A. F., 1997. Instruments for measuring quality of life in mental illnesses. In: Katschnig, H., Freeman, H., Sartorius, N. (Eds.), *Quality of Life in Mental Disorders*. John Wiley & Sons Ltd, Chichester, pp. 79-94.
- Markowitz, J. S., Weissman, M. M., Ouellette, R., Lish, J. D., Klerman, G. L., 1989. Quality of life in panic disorder. *Archives of General Psychiatry* 46, 984-992.
- McCrae, R. R., Costa, P. T., 1991. Adding Liebe und Arbeit: The full five-factor model and well-being. *Personality and Social Psychology Bulletin* 17(2), 227-232.
- Prosser, R., Rasbach, J., Goldstein, H., 1996. *MLn User's Guide*. Institute of Education, London.
- Pyne, J. M., Patterson, T. L., Kaplan, R. M., Gillin, J. C., Koch, W. L., Grant, I., 1997. Assessment of the quality of life of patients with major depression. *Psychiatric Services* 48(2), 224-230.
- Roberts, J. E., Kassel, J. D., 1997. Labile self-esteem, life stress, and depressive symptoms: Prospective data testing a model of vulnerability. *Cognitive Therapy and Research* 21, 569-589.

- Robins, L. N., Helzer, J. E., Orvaschel, H., Anthony, J. C., Blazer, D. G., Burnam, A., Burke, J. D., 1985. The Diagnostic Interview Schedule. In: Eaton, W. W., Kessler, L. G. (Eds.), *Epidemiologic Field Methods in Psychiatry: The NIMH Epidemiologic Catchment Area Program*. Academic Press, Orlando, pp. 143-170.
- Rollman, B. L., Block, M. R., Schulberg, H. C., 1997. Symptoms of major depression and tricyclic side effects in primary care patients. *Journal of General Internal Medicine* 12(5), 284-291.
- Spilker, B., 1990. *Quality of Life Assessments in Clinical Trials*. Raven Press, New York.
- Stoker, M. J., Dunbar, G. C., Beaumont, G., 1992. The SmithKline Beecham 'Quality of Life' scale: a validation and reliability study in patients with affective disorder. *Quality of Life Research* 1(6), 385-395.
- Sullivan, L. M., Dukes, K. A., Losina, E., 1999. An introduction to hierarchical linear modelling. *Statistics in Medicine* 18, 855-888.
- van der Zee, K. I., Sanderman, R., Heyink, J. W., de Haes, H., 1996. Psychometric qualities of the RAND 36-item health survey 1.0: a multidimensional measure of general health status. *International Journal of Behavioral Medicine* 3(2), 104-122.
- van Eck, M., 1996. *Stress, Mood, and Cortisol Dynamics in Daily Life*, Ph.D. dissertation, Maastricht University, Universitaire Pers, Maastricht.
- Verbrugge, L. M., 1985. Triggers of symptoms and health care. *Social Science and Medicine* 20(9), 855-876.
- Ware, J. E., 1996. The SF-36 Health Survey. In: Spilker, B. (Ed.), *Quality of Life and Pharmacoeconomics in Clinical Trials*, 2nd ed. Lippincott-Raven Publishers, Philadelphia, pp. 337-345.
- Watson, D., 1988. Intraindividual and interindividual analyses of positive and negative affect: their relation to health complaints, perceived stress, and daily activities. *Journal of Personality and Social Psychology* 54(6), 1020-1030.
- Watson, D., Clark, L. A., McIntyre, C. W., Hamaker, S., 1992. Affect, personality, and social activity. *Journal of Personality and Social Psychology* 63(6), 1011-1025.
- Watson, D., Clark, L. A., Tellegen, A., 1988. Development and validation of brief measures of positive and negative affect: the PANAS scales. *Journal of Personality and Social Psychology* 54(6), 1063-1070.
- Wells, K. B., Stewart, A., Hays, R. D., Burnam, M. A., Rogers, W., Daniels, M., Berry, S., Greenfield, S., Ware, J., 1989. The functioning and well-being of depressed patients. Results from the Medical Outcomes Study. *Journal of the American Medical Association* 262(7), 914-919.
- Wilson, K. C. M., Hopkins, R., deVries, M. W., Copeland, J. R. M., 1992. Research alliance and the limit of compliance: Experience Sampling with the depressed elderly. In: deVries, M. W. (Ed.), *The Experience of Psychopathology: Investigating Mental Disorders in Their Natural Settings*. Cambridge University Press, Cambridge, pp. 339-346.

PART III
MAIN STUDY (STUDY 2)

CHAPTER 6

Effects of antidepressant treatment on the quality of
daily life: An experience sampling study

Barge-Schaapveld, D. Q. C. M., Nicolson, N. A. Effects of antidepressant
treatment on the quality of daily life: an experience sampling study.
Journal of Clinical Psychiatry, under review.

Effects of antidepressant treatment on the quality of daily life: An experience sampling study

Background: Although some depression trials have included quality of life (QoL) as an outcome measure, assessments were retrospective and relatively infrequent. Because QoL varies in relation to everyday experience, intensive time-sampling approaches may be useful.

Method: The Experience Sampling Method (ESM) was used to assess effects of antidepressant treatment on the quality of life, as measured from moment to moment in daily life (mQoL), and related aspects of daily experience. Primary care patients with major depression ($N = 63$) were randomly assigned to imipramine (IMI) or placebo (PLA) treatment for 6 weeks, with possible prolongation to 18 weeks. A healthy control group ($N = 22$) provided normative data.

Results: Treatment-related increases in frequency or severity of physical complaints, including those not reported to the general practitioner as side effects, were associated with lowered mQoL; increased complaints were especially prominent in treatment drop-outs. Despite greater clinical improvement at week 6, IMI patients did not report greater increases than PLA patients in mean mQoL. However, IMI treatment stabilized mQoL fluctuations and led to reductions in time spent 'doing nothing'. Patients' decisions to prolong treatment depended on clinical improvement, mQoL changes, and specific early side effects. At 18 weeks, remitted patients still showed deficits on ESM daily life measures relative to healthy controls, even though QoL had returned to normal on retrospective measures.

Conclusion: ESM provides new insights in the effects of antidepressant treatment on daily life experiences and should therefore be considered as a supplement to conventional instruments in clinical trials.

INTRODUCTION

Quality of life (QoL) has become an accepted outcome measure in clinical drug trials, going beyond measures of symptom reduction. The acknowledged importance of QoL is reflected in an increasing trend over the past two decades to use QoL measures in clinical trials in all medical subdisciplines (Sanders et al., 1998). The same period has also seen a growing interest in the effects of drug treatments on QoL in depressive disorders. There are several reasons for this interest. First, depression has been recognized as a debilitating disorder with significant impairments in many areas of daily life (De Lisio et al., 1986; Wells et al., 1989), and treatment-related improvements in these areas are not adequately reflected in clinical rating scales. Another reason is that available antidepressant treatments, although comparable in terms of efficacy, may have different effects on QoL by virtue of their divergent side effect profiles (Song et al., 1993; Anderson and Tomenson, 1994). Finally, QoL evaluations assess the global impact of aspects related to side effect profile from the viewpoint of the patient and, hence, may provide better insight into the effects of different antidepressants than efficacy measures alone.

Following the approach taken by Sanders et al. (1998), we conducted a literature search over the period 1980-2000 and identified 42 randomized, controlled trials (RCTs) of pharmacological treatments in unipolar depressive disorders that included QoL assessments. Although only a small minority of these studies included a placebo arm, the nine studies that did reported significant differences between active and placebo groups on various dimensions of QoL, such as social relationships, life satisfaction, and leisure activities (Lydiard, 1994; Kocsis et al., 1997), thus supporting the hypothesis that antidepressants improve QoL in depressed patients. A number of questions remain, however.

Firstly, although side effects of antidepressants are widely believed to have a negative impact on the quality of life, research findings on this relationship are relatively meager (Healy, 1999). Because QoL is generally assessed at the end of treatment, when most side effects have subsided, information on the influence of early-appearing side effects is particularly scarce. Physical complaints experienced during the first week or two of treatment can contribute to poor compliance and early termination of treatment (Blackwell, 1982; Cookson, 1993), and it is thus important to investigate the frequency, severity, and QoL impact of early side effects as they are experienced in daily life.

Secondly, certain features of the QoL measures typically used in such studies place limitations on their ability to capture the full impact of the illness and its treatment on QoL.

All QoL measures, whether generic (e.g. SIP, Sechter et al., 1999) or depression-specific (e.g. Q-LES-Q, Leinonen et al., 1999), assess patients' QoL retrospectively, usually over the past week. In general, but even more so in depression research (Atkinson et al., 1997), retrospective measures are vulnerable to influences of current

affective state, forgetting, cognitive re-framing, and other sources of bias (Diener, 1994). This problem is compounded by the fact that most studies rely on single pre- and post-treatment measures. Both retrospective bias and infrequent measurement can reduce the reliability of QoL assessments.

A related limitation of conventional QoL measures is that they summarize average levels of well-being and thus cannot reveal how QoL varies in relation to everyday contexts and experiences. QoL is influenced by affect (Corrigan and Buican, 1995), physical symptoms (Pyne et al., 1997), and satisfaction with daily activities (Goethe and Fischer, 1995), all of which vary within the course of a single day. In other words, QoL has state as well as trait properties. Moreover, there is evidence that variability in QoL, from moment-to-moment or from day-to-day, is heightened in individuals most vulnerable to depression (Gable and Nezlek, 1998). Whether pharmacological treatment stabilizes QoL is as yet unknown, but this could prove to be a useful outcome measure.

Finally, RCTs have not yet clarified the time course over which aspects of QoL recover to 'normal' levels during antidepressant treatment. Six of the identified papers compared post-treatment findings to normative data; results indicated, for example, that QoL levels remained lower in clinically improved depressed patients than in a normative sample of the US (Walker et al., 1995) or Finland (Lonnqvist et al., 1994). However, the treatment duration in these studies ranged from 6 to 12 weeks, which might have been too short for QoL aspects to normalize. In addition, in only one study (Ravindran et al., 1999) was a group of healthy subjects recruited for direct comparison; in the other studies, differences in demographic characteristics, location, and time could have biased the comparisons with the controls.

The current study

To redress some of the limitations of earlier studies, the current study of the effects of pharmacological treatment on QoL used an intensive time-sampling approach. The experience sampling method (ESM) was developed to measure subjective experience over time and across situations (Csikszentmihalyi and Larson, 1987). During their normal daily routines, subjects complete frequent self-reports with respect to their mood, activity, location, and social context, in response to signals they receive at frequent but unpredictable intervals over a period of several days or a week. Advantages of the method include greater ecological validity and increased reliability, due to the repeated measurements and reduction in retrospective bias through time-sampling. Among many other applications, ESM has been used in research on psychiatric and psychosomatic disorders (deVries, 1992), including studies of QoL (Barge-Schaapveld et al., 1997; Barge-Schaapveld et al., 1999; deVries et al., 1999). To date, however, applications of ESM in the context of a clinical trial have been limited to a handful of studies: our initial study in a small sample of depressed outpatients treated with amitriptyline or

fluvoxamine (Barge-Schaapveld et al., 1995), a pilot investigation of the effect of relaxation training on asthma symptoms (Smyth et al., 1999), and two recent studies that used ESM to evaluate the effects of pharmacological treatments on nicotine craving and withdrawal symptoms during smoking cessation (Shiffman et al., 2000a; Shiffman et al., 2000b). Results obtained so far in ESM studies suggest that applying an intensive time-sampling approach in the context of a clinical trial may provide a better and more reliable understanding of the effects of treatment on the quality of daily life experience. In a previous analysis of ESM data collected in the same sample of depressed outpatients prior to treatment (Barge-Schaapveld et al., 1999), we found that self-reports of general well-being ('momentary QoL', or mQoL) showed considerable variation over the course of a day, with significantly greater within-person variability in depressed patients than in healthy controls. In both groups, positive and negative mood states, enjoyment of daily activities, and physical complaints had independent influences on mQoL. As expected, depressed patients had more negative (or less positive) scores on all of these variables than controls. In a different sample of depressed outpatients, we found that positive mood increased, negative mood decreased, and patterns of time use changed (time spent in chores increased and time spent in passive leisure decreased) following successful treatment with fluvoxamine or amitriptyline (Barge-Schaapveld et al., 1995).

The current study was designed to extend these findings in a number of ways:

- (1) Inclusion of assessments during the first week of treatment in the longitudinal design of the study allows investigation of the relationship between early side effects, mQoL, and subsequent termination of treatment. Patients with side effects were expected to experience lower levels of mQoL than patients without side effects (assuming that the positive effects of active treatment would not yet be apparent) and, as a consequence, be more likely to withdraw from treatment.
- (2) In contrast to an earlier ESM study (Barge-Schaapveld et al., 1995), the current study was placebo-controlled, so that observed changes in daily measures of QoL during treatment can be attributed with more confidence to the active drug (in this case, imipramine), and not (only) to spontaneous remission, placebo effects, or the effects of the ESM procedure itself. Imipramine was chosen as the active treatment because imipramine and related tricyclics remain the 'gold standard' for antidepressant efficacy (Gumnick and Nemeroff, 2000).
- (3) To determine whether mQoL stabilizes following active treatment, we compared intraindividual variability in mQoL from pre- to post-treatment in imipramine versus placebo groups. In the same sample, prior to treatment (Barge-Schaapveld et al., 1999), the magnitude of intraindividual variability was unrelated to the severity of depression, which would suggest that any decrease in variability found is more

likely to reflect an actual change in subject's experience of QoL than an increased reliability of the methodology in higher functioning individuals.

- (4) To obtain a better picture of the effects of extended treatment, additional sampling was done at 18 weeks. Comparison of ESM measures in patients treated for 18 weeks with those of healthy controls provides a measure of the efficacy of antidepressant treatment in normalizing QoL.

METHODS

Study design

The study was conducted in a primary care setting, in a sample of depressed outpatients presenting for treatment to their own general practitioners. During an initial baseline week, participants received no treatment of any form. Thereafter, patients were randomly assigned to twice-daily, double-blind treatment with either imipramine (starting dose of 50 mg/day, increased to 200 mg/day over the first week of treatment) or placebo (starting with one capsule per day, increased to 4 capsules over the first week of treatment). In cases of intolerance, the dose could be decreased to either 100 mg/day of imipramine or 2 placebo capsules per day. After 6 weeks, a decision was made concerning prolongation of double-blind treatment to 18 weeks, based on consensus between physician and patient. The possibility that some patients might thereby continue placebo treatment for up to 18 weeks was considered acceptable for the following reasons: (1) informed consent, (2) relatively mild symptomatology, (3) intensive clinical monitoring, (4) freedom to drop out, and (5) post-study access to standard treatment and continued follow-up. The study was approved by a medical ethics committee.

Subjects

Eighty-three patients with a DSM-III-R/DSM-IV diagnosis of current major depressive disorder were recruited in eight primary care practices in the Netherlands (for details concerning diagnosis and screening, see Barge-Schaapveld et al., 1999). Inclusion criteria were age between 18 and 65 years, a score at entry of ≥ 18 on the 17-item Hamilton Depression Rating Scale (HDRS) (Hamilton, 1960), and a score ≥ 4 on the Clinical Global Impression (CGI) (Guy, 1976). Exclusion criteria included current use of psychotropic medications and major medical disorders. All subjects gave written informed consent.

After exclusion of subjects who either did not meet all of the above criteria ($N = 9$) or had insufficient data during the ESM baseline sampling period ($N = 11$), 63 patients were included in the current analysis: 32 in the imipramine group (IMI) and 31 in the

placebo group (PLA) (for details about exclusion criteria and differences between included and excluded subjects, see Barge-Schaapveld et al., 1999). One PLA patient withdrew consent and three IMI patients dropped out due to adverse events during the first week of treatment. Of the 63 patients randomized, 49 (77.8%) completed the first 6 weeks of treatment. Subsequently, 35 patients agreed to prolong treatment, of whom 22 IMI and 13 PLA subjects (95.7% versus 50.0% of patients at week 6, respectively, $\chi^2 = 12.5, p < .001$). Eighty percent of these patients ($N = 28$: 17 IMI and 11 PLA) completed the prolongation phase through 18 weeks.

A control group of 22 healthy individuals, similar to the patient groups in sociodemographic characteristics, was recruited to provide normal reference values for ESM measures (for details, see Barge-Schaapveld et al., 1999).

Assessments

Clinical monitoring: efficacy and tolerability

The HDRS was administered by the treating physician (GP) at screening, baseline, and weeks 1, 2, 4, 6, 10, 14, and 18. At each visit, the GP asked whether the patient had experienced any unusual or unwanted signs or symptoms since the last visit. If so, start and stop dates were recorded as well as the severity of the symptom.

Retrospective QoL measures

Questionnaires completed with reference to the past week provided retrospective measures of quality of life. At the end of each sampling period, subjects were asked to rate the quality of their life on a 100-mm visual analogue scale (Andrews and McKennell, 1980) and to indicate their global life satisfaction on the Satisfaction with Life Scale (SWLS, Diener et al., 1985), which consists of five items (rated from 1 'strongly disagree' to 7 'strongly agree'). The validated Dutch version of the SF-36 Health Survey (van der Zee et al., 1996) was completed by a subset of 42 depressed subjects at some point during the baseline week.

ESM monitoring

After a briefing session in which a research nurse explained the procedure, patients completed ESM reports in response to signals from a programmed wristwatch at 10 semi-random intervals per day, between 07:30 and 22:30. ESM was conducted during 6 consecutive days during the baseline week, again during the last 3 days of the first week of treatment, and for 6 consecutive days in the sixth week of treatment. Finally, patients who remained in the treatment prolongation phase completed 6 consecutive days of ESM in week 18. An ESM self-report was considered valid if completed within 15 minutes after the signal. The protocol allowed only patients with a minimum of 30 valid reports to be randomized, so that by definition all subjects fulfilled this criterion in

the baseline week. ESM compliance remained acceptable throughout the study, with more than 80% of subjects in each of the repeated sampling periods completing valid reports in response to half or more of all signals.

Subjects were asked to complete ESM items with reference to the moment at which they received a signal (beep). At each beep, subjects rated their momentary QoL (mQoL) in response to the question 'In general, how is it going with you right now?'. Responses ranged from -3 ('very bad') to +3 ('very good'). In addition, subjects rated current mood, and enjoyment of the present activity on 7-point scales. Mood items were combined into separate scales for positive affective states (PA: items *energetic, cheerful, satisfied, alert, calm, enthusiastic, strong, and happy*) and negative states (NA: items *hostile, depressed, tense, lonely, anxious, insecure, guilty, harried, and irritable*). Physical complaints included three common side effects of imipramine: dry mouth, dizziness, and nausea (Cassano et al., 1994). In response to an open question, subjects provided a description of their current activity, which was later coded and collapsed into 8 categories. Only the category 'doing nothing' was used in the current analysis. The ESM procedure, questionnaire, and derived measures are described in greater detail elsewhere (Barge-Schaapveld et al., 1999; deVries et al., 1999).

Definition of measures

For each sampling week, ESM measures were averaged across all valid ESM records for each subject to obtain *mean levels* of mQoL, PA, NA, and *enjoyment of activities*. At baseline, mean mQoL was significantly associated with the other ESM measures (PA: $r = .55$, NA: $r = -.67$, enjoyment of activities: $r = .46$; $N = 63$; all p 's $< .001$; one-tailed tests). Mean mQoL also showed positive associations with all retrospective measures (mQoL with QoL VAS: $r = .42$, $p < .001$; mQoL with SWLS: $r = .33$, $p < .01$; mQoL with SF-36 mental subscale: $r = .29$, $p < .05$; one-tailed tests). These correlations support the construct validity of mQoL. Amount of *time spent doing nothing* was defined as the percentage of valid ESM records in which 'doing nothing' was specifically reported as the current activity. *Mean severity* of each *ESM complaint* (i.e., dry mouth, dizziness, and nausea) was obtained by averaging across all ESM records for each subject per sampling week. The *frequency* of each ESM complaint was defined as the percentage of records in which the complaint was reported present. Patients who showed an increase from pre-treatment baseline in either the mean severity or the frequency of a complaint were considered to have experienced a side effect of treatment (*ESM side effect*). Side effects reported to the general practitioner (*GP side effect*) as occurring in the same period over which ESM side effects were recorded were identified according to indicated start and stop dates.

Statistical analyses

Descriptive statistics are presented as means and standard deviations. Differences in continuous measures between groups over time were tested with ANOVA for repeated measures. Comparisons between groups at specific points in time were performed with two-sample *t*-tests for continuous variables and with χ^2 -tests for categorical variables. The Kappa statistic was calculated to assess agreement between GP and ESM side effect reports. Pearson correlations were used to assess the relationship between early-appearing side effects and changes in mQoL. To test the hypothesis that intraindividual variability in mQoL would stabilize following active treatment, we compared within-subject variance components estimated in a multilevel regression model (Barge-Schaapveld et al., 1999; Snijders and Bosker, 1999) for IMI and PLA patients at baseline and at week 6, and for controls. Unless otherwise noted, statistical tests were two-tailed, with $\alpha = .05$.

RESULTS

Patient characteristics

Patients ranged in age from 25 to 59 years (mean = 43.4 y). The majority were women (73%) and married (68%). Most had a regular job (44%) or were housewives (25%). There were no significant differences between the two treatment groups on either sociodemographic characteristics or initial HDRS ratings (IMI: 24.0 ± 3.5 , PLA: 23.5 ± 2.6 ; $t = -0.6$, $df = 61$, *ns*). Patients randomized to IMI ($N = 32$) were less likely to have had a previous episode of depression than those randomized to PLA ($N = 31$) (25.0% vs. 61.3%, $\chi^2 = 8.5$, $p < .01$).

Side effects of treatment

Differences between GP and ESM reports

More than 75% of all side effects reported to the GP occurred in the first week of treatment. Among the side effects most frequently reported to the GP during the three days at the end of the first week of treatment (corresponding to the ESM sampling period) were dry mouth, nausea, and dizziness, with all except dizziness reported by more IMI than PLA patients (see Table 1). Of the three complaints assessed with ESM, dry mouth and dizziness were reported by significantly more IMI than PLA patients.

The overall degree of agreement between GP and ESM assessments of side effects was surprisingly low (κ 's $< .30$). However, in at least half of the cases (Table 1, last column), GP ratings and ESM reports were in agreement on the presence or absence of

TABLE 1. Percentages of patients with specific side effects present in the first week of treatment.

	% patients with				% agreement between GP and ESM measures <i>N</i> = 59
	GP side effects		ESM side effects		
	IMI <i>N</i> = 29	PLA <i>N</i> = 30	IMI <i>N</i> = 29	PLA <i>N</i> = 30	
Dry mouth	41.4*	16.7	86.2***	46.7	59.3
Nausea	20.7*	3.3	41.4	36.7	62.7
Dizziness	13.8	10.0	72.4*	46.7	49.2

Differences between IMI and PLA groups (χ^2 -tests): * $p < .05$, ** $p < .01$.

TABLE 2. Correlations between ESM side effects (severity and frequency) and changes in mQoL (week 1) in treatment completers (*N* = 49) versus drop-outs (*N* = 10) (week 6).

	Side effect severity		Side effect frequency	
	Completers	Drop-outs	Completers	Drop-outs
Dry mouth	-.16	-.84*	.02	-.51
Nausea	-.27	-.22	-.29*	-.39
Dizziness	-.16	-.20	-.08	-.20

* $p < .05$, ** $p < .01$

side effects. In general, more patients reported ESM side effects than GP side effects, with increased dizziness, for example, experienced by 5 times as many subjects according to ESM reports (35 patients with ESM versus 7 with GP side effects). In general, ESM side effects were also reported as GP side effects when an increase from baseline occurred in the percentage of time spent with a complaint (see Figure 1a). Dry mouth was also more likely to be reported to the GP when a significant increase from baseline had occurred in the ESM-rated severity (see Figure 1b). However, patients with both ESM and GP side effects showed no greater decreases in mQoL than patients with ESM side effects only (dry mouth: $F = 1.8$, nausea: $F = 2.2$, dizziness: $F = 0.0$, all *ns*); in other words, a decrease in mQoL was no reason for patients to report side effects to the GP.

ESM side effects, mQoL, and early termination

To clarify the clinical relevance of the ESM side effects in the first treatment week, we examined their relationship to subsequent treatment drop-out. Of the 59 patients in the first week of treatment, 10 did not complete the entire 6-week treatment period (6 IMI and 4 PLA subjects). Associations between mQoL and both frequency and severity of complaints were greater in the drop-outs than in completers (see Table 2). In addition, drop-outs tended to report greater decreases in mQoL, from baseline to week 1,

FIGURE 1. Change from baseline to week 1 in ESM physical complaints. Patients who experienced an increase in ESM complaints and reported the same side effect to the GP are contrasted to patients who did not report ESM complaints as side effects to the GP. (a) Frequency of ESM complaints, (b) Severity of ESM complaints. Tests of group differences: * $p < .05$; *** $p < .001$.

TABLE 3. Intraindividual variance components for mQoL in the multilevel regression model.

	Variance estimates	
	Beep level	Day level
Depressed		
Imipramine		
Baseline	.57	.30
Week 6	.22	.10
Placebo		
Baseline	.58	.31
Week 6	.36	.26
Controls	.28	.20

than patients who subsequently completed 6 weeks of treatment ($-.33 \pm 0.9$ versus $.00 \pm .62$, $F = 2.1$, $p = .15$). This suggests that the impact of ESM side effects - including those not reported to the GP - on mQoL led patients to withdraw from treatment.

Changes at 6 weeks

Clinical efficacy, retrospective QoL and mQoL

At 6 weeks, both IMI and PLA groups showed clinical improvement (repeated measures ANOVA, Time effect: $F = 194.8$, $p < .001$), with HDRS scores declining on average to 8.9 ± 6.2 and 12.5 ± 6.3 , respectively. The IMI group showed significantly greater improvement than the PLA group (Group by Time effect: $F = 4.9$, $p < .05$). Despite greater clinical improvement, IMI patients did not report larger QoL increases than PLA patients on either QoL VAS (change: 27.3 ± 21.5 versus 21.0 ± 28.9 , $F = 0.7$, ns) or mQoL (change: 0.7 ± 0.7 versus 0.5 ± 1.0 , $F = 0.7$, ns). However, IMI patients did show greater increases in life satisfaction than PLA patients (increase in SWLS: 6.7 ± 7.8 versus 1.6 ± 6.3 , $F = 6.3$, $p < .05$).

mQoL variability

Active treatment was expected to decrease intraindividual fluctuations in mQoL. Results of the multilevel regression analysis supported this hypothesis. At week 6, variances in mQoL at both beep and day levels had significantly decreased from baseline in the combined patient groups (likelihood ratio tests, $p < .0001$). As shown in Table 3, active treatment had a stronger stabilizing effect, with greater decreases in beep level ($p < .001$) and day level ($p < .05$) variances in IMI than in PLA patients. At week 6, mQoL remained relatively unstable in PLA patients, as evidenced by significantly greater beep level variance in PLA than in controls ($p < .001$). In contrast, mQoL in the IMI group had stabilized by week 6, with both beep level ($p < .001$) and day level ($p < .01$) variance estimates even smaller than in healthy controls.

Other daily life measures

By week 6, significant changes from baseline in PA (repeated measures ANOVA, Time effect: $F = 16.6$, $p < .001$) and NA ($F = 19.5$, $p < .001$), but not in enjoyment of the current activity ($F = .01$, ns), were observed in both groups. The two treatment groups did not differ significantly from each other on any of these measures (Group by Time effect for PA: $F = .33$, NA: $F = .21$, and enjoyment of activities: $F = .84$, all ns).

Time spent 'doing nothing'

Previous ESM studies showed a link between inactivity and low mQoL (Barge-Schaapveld et al., 1997; Barge-Schaapveld et al., 1999). The percentage of patients who reported 'doing nothing' as their current activity at some point during

ESM sampling decreased significantly from baseline to week 6 in the IMI (87.5% versus 43.5% respectively, $\chi^2 = 12.1$, $p < .001$) but not in the PLA group (74.2% versus 61.5% respectively, $\chi^2 = 1.1$, ns). In order to compare the magnitude of these changes, we identified the percentage of patients per treatment group who reported some inactivity at baseline but no inactivity at week 6; this percentage was twice as high in the IMI as in the PLA group (52.2% vs. 26.9% respectively, $\chi^2 = 2.0$, $p = .07$). In other words, more IMI than PLA patients reduced their level of inactivity to 0% over the course of 6 weeks. There was, however, no significant difference in the reduction in percentage of time spent doing nothing between IMI and PLA groups ($-2.1\% \pm 6.6$ versus $-3.7\% \pm 6.0$, $F = 0.8$, ns).

Changes with prolonged treatment (18 weeks)

Factors related to prolongation

As expected, the 35 patients who entered the treatment prolongation phase had shown greater decreases in HDRS scores than patients who stopped at 6 weeks (-15.7 ± 5.1 versus -6.5 ± 6.5 , $F = 27.8$, $p < .001$). Prolongers had also experienced a greater increase from baseline in levels of mQoL than non-prolongers (0.8 ± 0.8 versus 0.1 ± 0.8 , $F = 7.9$, $p < .01$). Contrary to expectation, prolongers had experienced *greater* increases than non-prolongers in the ESM complaint 'dry mouth' during the first week of treatment (increase in frequency: $31.0\% \pm 39.2$ versus $7.4\% \pm 32.6$, $F = 5.9$, $p < .05$; increase in severity: 1.0 ± 1.4 versus 0.2 ± 1.2 , $F = 4.7$, $p < .05$). This was specifically true for prolongers relative to non-prolongers on imipramine (frequency: $F = 5.3$, severity: $F = 5.1$, both p 's $< .05$), but not on placebo (frequency: $F = 0.4$, severity: $F = 0.1$, ns). Experience of other side effects did not differentiate prolongers from non-prolongers. Taken together, these results suggest that degree of clinical improvement, mQoL changes, and specific side effects may all have influenced the decision to prolong treatment.

Normalization

There was no difference in clinical severity between IMI and PLA groups at week 18 (HDRS: 4.9 ± 6.7 versus 3.8 ± 5.3 , $F = .03$, ns). Of the 28 patients who completed treatment, 23 were considered to be clinically remitted at 18 weeks (HDRS ≤ 7) (IMI: 14/17, PLA: 9/11; $\chi^2 = 0.0$, ns). To determine whether quality of life measures achieved normal levels, measures in the remitted patients were contrasted to those in the healthy control group.

Remitted patients and controls reported similar levels of QoL VAS (75.0 ± 19.1 versus 76.5 ± 15.6 , $t = 0.3$, $df = 43$, ns) and SWLS (25.6 ± 7.3 versus 27.5 ± 6.8 , $t = 0.9$, $df = 43$, ns). However, remitted patients still had significantly lower mQoL (see Figure 2). Only 10 of the 23 patients in remission (5 in each treatment arm) had mean mQoL

FIGURE 2. Mean levels of ESM variables in remitted patients at week 18 ($N = 23$) and in control subjects ($N = 22$). mQoL: $t = 2.8$, $df = 31$. PA: $t = 1.9$, $df = 43$. NA: $t = -2.8$, $df = 24$. Enjoyment: $t = 2.3$, $df = 35$. * $p < .05$, ** $p < .01$.

levels at or above the lower bound (mQoL = 1.86) of the 95%-confidence interval for healthy controls. Mean levels of other daily life measures in remitted patients were also significantly different from those of healthy controls (see Figure 2).

Prior to treatment, a greater percentage of patients than controls had reported at times to be doing nothing. In addition, depressed subjects had spent a greater percentage of time in doing nothing than controls (Barge-Schaapveld et al., 1999). At 18 weeks, a similar percentage of remitted patients and controls reported doing nothing at some point during the sampling period (47.8% versus 50.0% respectively, $\chi^2 = 0.2$, ns). Moreover, the percentage of time in doing nothing no longer differed between the two groups (4.9 ± 9.0 versus 2.2 ± 3.3 respectively, $t = -1.3$, $df = 28$, ns).

Depressed patients had reported both greater frequency and intensity of physical complaints, even before treatment, than healthy controls (Barge-Schaapveld et al., 1999). At 18 weeks, significantly more remitted patients than healthy controls still reported dizziness (30.4% versus 4.5%, $\chi^2 = 5.2$, $p < .05$) or dry mouth (65.2% versus 27.3%, $\chi^2 = 6.5$, $p < .01$) at some point during ESM sampling. None of these remitted patients had reported dizziness, and only six (26.1%) had reported dry mouth as GP side effect in that week. Dry mouth and dizziness also occurred with a higher frequency (dry mouth: 42.3 ± 46.4 versus 2.2 ± 6.1 , $t = -4.1$, $df = 23$, $p < .001$; dizziness: 12.5 ± 26.4 versus 0.4 ± 2.0 , $t = -2.2$, $df = 22$, $p < .05$) and were rated as more severe in the re-

mitted than in the control group (dry mouth: 2.0 ± 1.3 versus 1.0 ± 0.1 , $t = -3.6$, $df = 22$, $p < .01$; dizziness: 1.2 ± 0.5 versus 1.0 ± 0.0 , $t = -2.1$, $df = 22$, $p < .05$).

In summary, despite normalized QoL on global retrospective measures, remitted patients still differed from healthy controls in most aspects of daily QoL.

DISCUSSION

Most antidepressant drug studies rely primarily on clinician measures such as the HDRS. However, self-rating scales can provide important additional information for therapy evaluation as they reflect the patient's personal experience of illness and recovery (Möller, 2000). In the current study, intensive ESM monitoring in the context of daily life revealed effects of depression and antidepressant treatment on well-being, mood states, physical complaints, enjoyment of activities, and patterns of time use - information that could not have been obtained with conventional instruments. More specifically, this study provides new information concerning early side effects, changes in daily experience associated with treatment and with clinical improvement, intraindividual variability in the state of well-being, and normalization of daily experience during sustained treatment.

As expected, more IMI than PLA patients reported side effects in the first week of treatment; IMI side effects were also more frequent and more severe. Only a small percentage of patients who showed an increase in specific physical complaints on ESM measures reported these as 'side effects' in the same period to the GP. ESM side effects were associated with decrements in mQoL, and patients who reported frequent and severe ESM side effects in the first week were overrepresented among subsequent treatment drop-outs. It is important to note that the study was not designed to determine whether ESM-reported side effects might better predict treatment drop-out than reports to the GP. According to the standard protocol for assessing adverse events in clinical trials, side effects that lead to treatment discontinuation must be registered as GP side effects. This means, by definition, that there is a coupling between GP side effects and subsequent drop-out. Meaningful comparison of the two side effect measures is therefore difficult. However, the lack of any association between mQoL and side effects reported to the GP suggests that clinicians were unaware of side effects of treatment that had a negative impact on patients' daily quality of life.

Whether or not patients report side effects to the GP also depends to some extent on factors present at the time of the assessment (Anderson and Testa, 1994) or personality characteristics of the patient (Davis et al., 1995). Based on the current results, we suggest that such problems can be reduced by obtaining self-reports from patients in real time, in their everyday environments, and by asking patients to rate physical complaints (often present prior to any treatment) instead of side effects. In future studies, ESM

could be useful in describing the side effect profiles of different antidepressant drugs and their relative impacts on QoL.

The current findings also point to the potential usefulness of ESM measures in understanding treatment adherence. As the decision to prolong treatment was left up to the patient and the GP, it is not surprising that prolongers showed greater clinical improvement and greater increases in mQoL than non-prolongers. It is noteworthy, however, that prolongers, specifically those on IMI, had experienced more frequent and severe dry mouth (a typical imipramine side effect) in the first week of treatment than non-prolongers. Some authors have questioned the integrity of the double-blind procedure (Antonuccio et al., 1999): if patients can correctly guess the treatment they are receiving due to experienced side effects, they may be more likely to expect positive results. We speculate that these positive expectations might have led patients in our study to opt for a prolongation of treatment.

At 6 weeks, IMI patients showed no greater improvements than PLA patients on the ESM measures of mQoL, mood measures, and enjoyment, even though the active treatment did result in greater clinical improvement on the HDRS. IMI was more effective than PLA in decreasing mQoL within-subject variability and time spent in inactivity. Both the relatively small number of patients in the sample (despite the large number of observations per subject) and the choice of antidepressant may have contributed to the subtle nature of the observed differences between IMI and PLA treatments. Placebo-controlled studies that have reported significant effects of antidepressant treatment on QoL outcome measures (Dubini et al., 1997; Lydiard et al., 1997; Lenderking et al., 1999) included at least 100 patients per treatment group. Furthermore, although imipramine remains a 'gold standard' for clinical efficacy, other RCT's have been unable to demonstrate an advantage of this drug over placebo in QoL outcomes (see, for example, Philipp et al., 1999).

At 18 weeks, ESM measures still differed in clinically remitted patients from those of healthy individuals, even though QoL had returned to normal on retrospective measures. Normalization in daily life appears to require more time than results obtained with conventional measures would suggest. It is also possible that the remaining differences in the experience of daily life reflect either 'scars' from the depressive episode or trait-like aspects, which may in turn predispose remitted patients to subsequent episodes. The investigation of daily QoL measures in future recurrence-prevention studies may shed more light on these different possibilities. Even though most of the completers were in clinical remission at 18 weeks, only a minority had achieved normal levels of daily QoL by that time, suggesting that currently used criteria for response in depression may not be sufficient to provide evidence of normalization in daily life. These results underscore the need to rethink the current reliance on clinical scales as the sole measure of treatment success in depression (Rush, 1996).

Aspects of the study design place some limits on the conclusions. Firstly, we assessed momentary quality of life with a single item (mQoL). Although the observed correlations between average mQoL scores and retrospective QoL measures (see Methods) support the construct validity of mQoL, a multi-item measure would have psychometric advantages in future studies (see Diener, 1984). Furthermore, multilevel regression results as well as the pattern of correlations among ESM measures indicate that mQoL represents more than mood alone (Barge-Schaapveld et al., 1999). Secondly, patients provided ESM data during four discrete sampling periods throughout the treatment. Continuous ESM sampling could yield more conclusive information about improvement curves, but the research burden for subjects might become unacceptably high. Future studies should weigh the option of sampling less frequently per day over longer periods of time; evidence that continuous long-term sampling may be feasible comes from an ESM study of migraine patients, in which ESM reports were obtained 6 times a day for 10 weeks (Honkoop et al., 1999). Thirdly, the decision-making process about prolonging treatment beyond 6 weeks (based on the consensus reached by GP and patient), although similar to real-life clinical practice, makes it difficult to interpret the findings at 18 weeks.

Experience to date shows that ESM is feasible in the context of a clinical trial. Depressed patients, with the possible exception of the most severely depressed (Kraan et al., 1992), are willing and able to comply with repeated sampling periods (Barge-Schaapveld et al., 1995; Barge-Schaapveld et al., 1999). Although, in this particular study, the observed advantages of antidepressant treatment over placebo on quality of life measures were subtle, the potential usefulness of ESM measures in understanding treatment compliance, termination, and outcome has been highlighted. In light of the growing interest in QoL in the course and outcome of depressive disorders, we believe that more widespread use of time-sampling methods as a supplement to conventional approaches will prove useful for clinicians as well as researchers.

REFERENCES

- Anderson, I. M., Tomenson, B. M., 1994. The efficacy of selective serotonin re-uptake inhibitors in depression: a meta-analysis of studies against tricyclic antidepressants. *J Psychopharmacol* 8(4), 238-249.
- Anderson, R. B., Testa, M. A., 1994. Symptom distress checklists as a component of quality of life measurement: comparing prompted reports by patient and physician with concurrent adverse event reports via the physician. *Drug Information Journal* 28, 89-114.
- Andrews, F. M., McKennell, A. C., 1980. Measures of self-reported well-being: their affective, cognitive, and other components. *Social Indicators Research* 8, 127-155.
- Antonuccio, D. O., Danton, W. G., DeNelsky, G. Y., Greenberg, R. P., Gordon, J. S., 1999. Raising questions about antidepressants. *Psychother Psychosom* 68(1), 3-14.
- Atkinson, M., Zibin, S., Chuang, H., 1997. Characterizing quality of life among patients with chronic mental illness: a critical examination of the self-report methodology. *Am J Psychiatry* 154(1), 99-105.

- Barge-Schaapveld, D. Q. C. M., Nicolson, N. A., Berkhof, J., deVries, M. W., 1999. Quality of life in depression: daily life determinants and variability. *Psychiatr Res* 88, 173-189.
- Barge-Schaapveld, D. Q. C. M., Nicolson, N. A., Delespaul, P. A. E. G., deVries, M. W., 1997. Assessing daily quality of life with the Experience Sampling Method. In: Katschnig, H., Freeman, H., Sartorius, N. (Eds.), *Quality of Life in Mental Disorders*. John Wiley & Sons Ltd, Chichester, pp. 95-107.
- Barge-Schaapveld, D. Q. C. M., Nicolson, N. A., Gerritsen van der Hoop, R., deVries, M. W., 1995. Changes in daily life experience associated with clinical improvement in depression. *J Affect Dis* 34, 139-154.
- Blackwell, B., 1982. Antidepressant drugs: side effects and compliance. *J Clin Psychiatry* 43(11 Pt 2), 14-21.
- Cassano, G. B., Toni, C., Petracca, A., Deltito, J., Benkert, O., Curtis, G., Hippus, H., Maier, W., Shera, D., Klerman, G., 1994. Adverse effects associated with the short-term treatment of panic disorder with imipramine, alprazolam or placebo. *Eur Neuropsychopharmacol* 4, 47-53.
- Cookson, J., 1993. Side-effects of antidepressants. *Br J Psychiatry* 163(Suppl. 20), 20-24.
- Corrigan, P. W., Buican, B., 1995. The construct validity of subjective quality of life for the severely mentally ill. *J Nerv Ment Dis* 183, 281-285.
- Csikszentmihalyi, M., Larson, R., 1987. Validity and reliability of the Experience Sampling Method. *J Nerv Ment Dis* 175(9), 526-537.
- Davis, C., Ralevski, E., Kennedy, S. H., Neitzert, C., 1995. The role of personality factors in the reporting of side effect complaints to moclobemide and placebo: a study of healthy male and female volunteers. *J Clin Psychopharmacol* 15(5), 347-352.
- De Lisio, G., Maremmi, I., Perugi, G., Cassano, G. B., Deltito, J., Akiskal, H. S., 1986. Impairment of work and leisure in depressed outpatients: a preliminary communication. *J Affect Disord* 10, 79-84.
- deVries, M. W., 1992. *The Experience of Psychopathology: Investigating Mental Disorders in Their Natural Settings*. Cambridge University Press, Cambridge.
- deVries, M. W., Delespaul, P. A. E. G., Nicolson, N. A., 1999. Experience Sampling Method (ESM). In: Salek, S. (Ed.), *Compendium of Quality of Life Instruments*. John Wiley & Sons, Chichester, pp. 2L:6; 2L:6a.
- Diener, E., 1984. Subjective well-being. *Psychological Bulletin* 95(3), 542-575.
- Diener, E., 1994. Assessing subjective well-being: progress and opportunities. *Soc Ind Res* 31, 103-157.
- Diener, E., Emmons, R. A., Larsen, R. J., Griffin, S., 1985. The Satisfaction With Life Scale. *Journal of Personality Assessment* 49(1), 71-75.
- Dubini, A., Bosc, M., Polin, V., 1997. Noradrenaline-selective versus serotonin-selective antidepressant therapy: differential effects on social functioning. *J Psychopharmacol* 11(4), S17-S23.
- Gable, S. L., Nezlek, J. B., 1998. Level and instability of day-to-day psychological well-being and risk for depression. *J Pers Soc Psychol* 74(1), 129-138.
- Goethe, J. W., Fischer, E. H., 1995. Functional impairment in depressed inpatients. *J Affect Disord* 33, 23-29.
- Gumnick, J. F., Nemeroff, C. B., 2000. Problems with currently available antidepressants. *J Clin Psychiatry* 61(Suppl 10), 5-15.
- Guy, W., 1976. *ECDEU Assessment Manual for Psychopharmacology*. US Department of Health, Education and Welfare, Rockville, MD, pp. 59-70.
- Hamilton, M., 1960. A rating scale for depression. *J Neurol Neurosurg Psychiatr* 23, 56-62.
- Healy, D., 1999. The three faces of the antidepressants: a critical commentary on the clinical-economic context of diagnosis. *J Nerv Ment Dis* 187(3), 174-180.
- Honkoop, P. C., Sorbi, M. J., Godaert, G. L., Spierings, E. L., 1999. High-density assessment of the IHS classification criteria for migraine without aura: a prospective study. *Cephalalgia* 19(4), 201-206.

- Kocsis, J. H., Zisook, S., Davidson, J., Shelton, R., Yonkers, K., Hellerstein, D. J., Rosenbaum, J., Halbreich, U., 1997. Double-blind comparison of sertraline, imipramine, and placebo in the treatment of dysthymia: psychosocial outcomes. *Am J Psychiatry* 154(3), 390-395.
- Kraan, H., Meertens, H., Hilwig, M., Volovics, L., Dijkman-Caes, C. I. M., Portegijs, P., 1992. Selecting measures, diagnostic validity and scaling in the study of depression. In: de Vries, M. W. (Ed.), *The Experience of Psychopathology: Investigating Mental Disorders in Their Natural Settings*. Cambridge University Press, Cambridge, pp. 324-338.
- Leinonen, E., Skarstein, J., Behnke, K., Agren, H., Helsdingen, J. T., 1999. Efficacy and tolerability of mirtazapine versus citalopram: a double-blind, randomized study in patients with major depressive disorder. Nordic Antidepressant Study Group. *Int Clin Psychopharmacol* 14(6), 329-337.
- Lenderking, W. R., Tennen, H., Nackley, J. F., Hale, M. S., Turner, R. R., Testa, M. A., 1999. The effects of venlafaxine on social activity level in depressed outpatients. *J Clin Psychiatry* 60(3), 157-163.
- Lonnqvist, J., Sintonen, H., Syvalahti, E., Appelberg, B., Koskinen, T., Mannikko, T., Mehtonen, O. P., Naarala, M., Sihvo, S., Auvinen, J., Pitkanen, H., 1994. Antidepressant efficacy and quality of life in depression: a double-blind study with moclobemide and fluoxetine. *Acta Psychiatr Scand* 89, 363-369.
- Lydiard, R. B., 1994. Sertraline vs amitriptyline and quality of life: a double-blind, placebo-controlled study. *Neuropsychopharmacol* 10(3S/part 2), S163.
- Lydiard, R. B., Stahl, S. M., Hertzman, M., Harrison, W. M., 1997. A double-blind, placebo-controlled study comparing the effects of sertraline versus amitriptyline in the treatment of major depression. *J Clin Psychiatry* 58(11), 484-491.
- Möller, H. J., 2000. Rating depressed patients: observer- vs self-assessment. *Eur Psychiatry* 15(3), 160-172.
- Philipp, M., Kohnen, R., Hiller, K. O., 1999. Hypericum extract versus imipramine or placebo in patients with moderate depression: randomised multicentre study of treatment for eight weeks. *BMJ* 319(7224), 1534-1538.
- Pyne, J. M., Patterson, T. L., Kaplan, R. M., Gillin, J. C., Koch, W. L., Grant, I., 1997. Assessment of the quality of life of patients with major depression. *Psychiatr Serv* 48(2), 224-230.
- Ravindran, A. V., Anisman, H., Merali, Z., Charbonneau, Y., Telner, J., Bialik, R. J., Wiens, A., Ellis, J., Griffiths, J., 1999. Treatment of primary dysthymia with group cognitive therapy and pharmacotherapy: clinical symptoms and functional impairments. *Am J Psychiatry* 156(10), 1608-1617.
- Rush, A. J., 1996. Assessing outcome in practice: a paradigm shift? *Curr Opin Psychiatry* 9, 1-2.
- Sanders, C., Egger, M., Donovan, J., Tallon, D., Frankel, S., 1998. Reporting on quality of life in randomised controlled trials: bibliographic study. *BMJ* 317(7167), 1191-1194.
- Sechter, D., Troy, S., Paternetti, S., Boyer, P., 1999. A double-blind comparison of sertraline and fluoxetine in the treatment of major depressive episode in outpatients. *Eur Psychiatry* 14(1), 41-48.
- Shiffman, S., Elash, C. A., Paton, S. M., Gwaltney, C. J., Paty, J. A., Clark, D. B., Liu, K. S., Di Marino, M. E., 2000a. Comparative efficacy of 24-hour and 16-hour transdermal nicotine patches for relief of morning craving. *Addiction* 95(8), 1185-1195.
- Shiffman, S., Johnston, J. A., Khayrallah, M., Elash, C. A., Gwaltney, C. J., Paty, J. A., Gnys, M., Evoniuk, G., DeVaugh-Geiss, J., 2000b. The effect of bupropion on nicotine craving and withdrawal. *Psychopharmacology (Berl)* 148(1), 33-40.
- Smyth, J. M., Soefer, M. H., Hurewitz, A., Stone, A. A., 1999. The effect of tape-recorded relaxation training on well-being, symptoms, and peak expiratory flow rate in adult asthmatics: a pilot study. *Psychology and Health* 14, 487-501.
- Snijders, T. A. B., Bosker, R. J., 1999. *Multilevel analysis: an Introduction to Basic and Advanced Multilevel Modeling*. SAGE Publications, London.
- Song, F., Freemantle, N., Sheldon, T. A., House, A., Watson, P., Long, A., Mason, J., 1993. Selective serotonin reuptake inhibitors: meta-analysis of efficacy and acceptability. *Bmj* 306(683), 683-687.

- van der Zee, K. I., Sanderman, R., Heyink, J. W., de Haes, H., 1996. Psychometric qualities of the RAND 36-item health survey 1.0: a multidimensional measure of general health status. *International Journal of Behavioral Medicine* 3(2), 104-122.
- Walker, V., Streiner, D. L., Novosel, S., Rocchi, A., Levine, M. A. H., Dean, D. M., 1995. Health-related quality of life in patients with major depression who are treated with moclobemide. *J Clin Psychopharmacol* 15(4 (Suppl. 2)), 60S-67S.
- Wells, K. B., Stewart, A., Hays, R. D., Burnam, M. A., Rogers, W., Daniels, M., Berry, S., Greenfield, S., Ware, J., 1989. The functioning and well-being of depressed patients. Results from the Medical Outcomes Study. *Journal of the American Medical Association* 262(7), 914-919.

PART III
MAIN STUDY (STUDY 2)

CHAPTER 7

The everyday experience of
two depressed patients: A responder and a
non-responder to treatment

The everyday experience of two depressed patients: A responder and a non-responder to treatment

INTRODUCTION

In spite of traditional prejudices against the case study strategy (e.g., lack of rigor, little basis for scientific generalization), case examples have obtained a distinctive place in evaluation research (Yin, 1994). The two examples described in this chapter are by no means 'exemplary', but they do illustrate the quantitative results presented in the foregoing chapters and provide insight into the complexities that can be hidden in group-level results, which are briefly summarized hereafter.

In both Chapters 3 & 4, compliance with ESM was described as high across the sampling periods. In addition, average delay between the beep and the response time was found to decrease over time in responders but not in non-responders to treatment, and in depressed but not in healthy subjects. In Chapter 6, treatment response was accompanied by an increase in levels and a decrease in fluctuations of mQoL. Moreover, decrements in mQoL during the first week of treatment were related to ESM but not to GP side effects and led patients to withdraw from treatment. Overall, there were more ESM than GP side effects reported. Finally, as discussed in Chapter 5, depressed patients differed from healthy individuals in the percentage of time spent 'doing nothing'. Data presented in Chapter 6 showed that responders to treatment reported significant reductions in average time spent 'doing nothing' compared to non-responders.

The main objective of the current chapter is to illustrate the value of ESM in translating response to treatment into everyday experience, thereby providing clues to a better understanding of the impact of depression and its treatment.

METHODS

Subjects

The two subjects participated in Study 2 (see Chapters 4-6) and were both randomized to imipramine treatment. The first case (*Suzanne*) was chosen as an example of a treatment followed over the course of 18 weeks. The second case concerns a non-responder, *Catherine*, who was withdrawn from the study due to non-adherence to treatment after 16 days on imipramine.

Case 1. Suzanne is a 38-year old woman who is suffering from recurrent major depression superimposed on dysthymic disorder. She was 21 at the time of her first episode. Her current episode started about 10 months prior to her participation in the study. She is married and has three children: two boys, aged 16 and 12, and a girl of 5 years old. Her main occupation is homemaker, but she also assists for several hours in the week in a bakery. In addition, Suzanne works as a volunteer at her daughter's primary school.

Case 2. Catherine is a 35-year old woman who is divorced and lives with her 8-year-old daughter. As long as she can remember, she has dreaded being alone. After an unhappy marriage that lasted 10 years, Catherine experienced a first depressive episode two years ago, in addition to developing symptoms of panic disorder. She is currently unemployed but receives social benefits. Catherine has a new boyfriend who is 10 years younger than she is. He stays regularly at her place. At the time of the study, she reports being nervous and depressed most of the time and only occasionally happy or satisfied. Her current episode started quite suddenly a few weeks prior to the study. The only medication she is taking is an oral contraceptive, which she has taken for more than 4 years.

Assessments

ESM monitoring. The ESM sampling periods were conducted according to the procedure described in Chapter 6 (section 6.2, 'Methods'). In addition to the ESM measures described in that chapter (i.e. mQoL, PA, NA, enjoyment and type of activities, frequency and severity of each ESM complaint), other ESM items were also considered here (see Appendix 2). At each beep, subjects were asked whether they were brooding about something, and if so they were requested to describe these thoughts. In response to open questions, subjects also provided a description of where and with whom they were at the time of the beep. Finally, they were asked to report any positive or negative event that had occurred since the last beep.

Clinical monitoring. The assessments of patients' clinical response was based on the HDRS (Hamilton, 1960), as rated by the treating physician (GP) at baseline, week 6, and week 18. Response to treatment was defined as 50% or greater reduction from baseline in HDRS scores. Throughout the study, the GP asked whether the patient had experienced any unusual or unwanted signs or symptoms.

Retrospective QoL monitoring. The overall level of QoL was rated retrospectively at the end of each ESM sampling period on the QoL VAS, a 100-mm visual analogue scale (Andrews and McKennell, 1980).

RESULTS

Suzanne: a responder to treatment

Clinical follow-up. At baseline, Suzanne is considered ‘markedly ill’ by her treating physician, with a rating of 28 on the HDRS. At that time, Suzanne herself reports being completely worn out, often depressed, never calm or satisfied, and only rarely happy. She rates her QoL during the baseline week with a mark at 29mm from the ‘worst QoL you can imagine for yourself’ on the 100-mm QoL VAS. According to protocol, her dose is increased to 200 mg of imipramine over the course of a week and Suzanne is kept at that dose for the remainder of the study. At the end of the first week, her score on the HDRS decreases to 20, providing a first hint of response, although she herself reports no change on the QoL VAS (27mm). After 6 weeks, Suzanne has shown a drop of more than 50% from baseline in her depressive symptoms (HDRS is now 8), and is therefore considered a responder to treatment. Her rating on the QoL VAS now shifts toward the ‘best QoL you can imagine for yourself’ (78mm). In mutual agreement with her physician, she decides to prolong her participation in the study for another 12 weeks. At the end of this treatment period, her depressive symptoms show a further reduction (HDRS is now 2). However, no further improvement is seen on the QoL VAS (79mm). Throughout the entire study, she has not reported any adverse events to the GP.

ESM data. Suzanne completes an acceptable number of experience sampling report forms across the four sampling periods, with higher completion rates in the first two periods (above 80%) than in the last two periods (above 50%). In the first sampling period, it takes Suzanne on average 1.78 min to complete a self-report form. Average response time decreases to 1.47 min during week 6 and to 0.12 min in the 18th week of treatment.

Suzanne’s levels of mQoL throughout the four sampling periods are shown in Figure 1; for comparison purposes QoL VAS scores, transformed to (–3,3) scale as described in Chapter 4, are also shown. During the pre-treatment baseline week her level of mQoL fluctuates between –2 and 1. The worst mQoL moments occur when she is brooding about her relationship with her husband. This usually happens when she is doing household chores. During these moments she always reports having a headache. The best mQoL moments during this week occur while Suzanne is engaged in activities she enjoys doing (e.g. reading, dining out, watching T.V.). During these moments, Suzanne has no physical complaints.

During the first week of treatment, Suzanne experiences even more swings in her mQoL states than during the baseline sampling week. The mQoL level is not context-dependent, as she spends most of her time during this period at home doing chores (73.1%). Although the percentage of time with headache is reduced from baseline,

FIGURE 1. Levels of mQoL (—) and QoL VAS (---) reported by Suzanne during the four experience sampling periods (6 days pre-treatment, 3 days in the 1st week of treatment, 6 days in the 6th week of treatment, and 6 days in the 18th week of treatment) throughout the study.

FIGURE 2. Frequency (as % of ESM reports; bar) and mean severity (○) of headache and dry mouth reported by Suzanne during the four experience sampling periods. Per 1 = Period 1 (Baseline), Per 2 = Period 2 (Week 1), Per 3 = Period 3 (Week 6), Per 4 = Period 4 (Week 18).

Suzanne experiences moderate levels of dry mouth more than half of the time (56.5%) (see Figure 2 for the frequency and severity of headache and dry mouth across the sampling periods).

In the sixth week of treatment, Suzanne experiences higher average levels of mQoL than at baseline. During this week, she has four moments of high mQoL, characterized by high levels of positive affect ($PA > 4$). However, a negative event may still precipitate a drop in mQoL, as is the case on Tuesday evening when Suzanne has an argument with her husband. While watching T.V., Suzanne reports very severe headache and dry mouth, and experiences high levels of negative affect. This carries over to the following day, as she broods about her relationship with her husband while doing chores alone at home.

After 18 weeks of treatment, Suzanne's average level of mQoL approaches 'normal' (the lower bound of the 95%-confidence interval for healthy controls = 1.86, see Chapter 6). Even though her marital problems are not resolved, she manages to cope with them. Negative interactions with her husband no longer precipitate low mQoL. On Monday evening, for example, she has an argument with her husband but rates her mQoL as 2. Suzanne continues to experience dry mouth throughout the entire week.

Catherine: a non-responder to treatment

Clinical follow-up. At baseline, Catherine is reported to be 'markedly ill' by her GP and is rated 25 on the HDRS. When asked to rate her QoL over the past week on the VAS, Catherine marks 9mm from 'the worst QoL you can imagine for yourself'. This rating seems to be influenced by events of the previous day (as can be seen in Figure 3) and may not be representative for the entire week. She starts with 50 mg of imipramine in the evening. But from that first day she reports excessive transpiration, accompanied three days later by vomiting; both complaints last until the end of her participation in the study. In both instances, the physician regards the relationship with the drug to be probable. Therefore, instead of increasing the dose of imipramine over the course of the first week to 200 mg as per protocol, the physician decides to keep Catherine on a dose of 50 mg/day. Although her HDRS is unchanged (24), she rates her QoL as slightly better (24mm) from baseline. At the end of this first week, Catherine does not return any capsule of study medication to the physician, stating that she has thrown all remaining capsules away. During the second week, the dose is gradually increased to 100 mg of imipramine, which Catherine receives according to the physician for another 8 days. However, as Catherine returns only 14 (35%) capsules instead of the 24 (60%) that are expected on the basis of the dosage schedule, she is withdrawn from the study due to non-adherence with the prescribed medication.

ESM data. Catherine is compliant with respect to ESM, completing 63.3% of the reports pre-treatment and 80% in the first week of treatment. The mean time she

FIGURE 3. Levels of mQoL (—) and QoL VAS (---) reported by Catherine during the two experience sampling periods (6 days pre-treatment, 3 days in the 1st week of treatment) throughout the study.

FIGURE 4. Frequency (as % of ESM reports; bar) and mean severity (o) of complaints that Catherine reported during the two experience sampling periods throughout the study.

requires to respond to a self-report is 1.21 min pre-treatment and does not change over time (1.25 min on treatment).

Catherine's levels of mQoL during the sampled days are shown in Figure 3. On average, Catherine experiences a lower level of mQoL on treatment than prior to treatment. Her best moment pre-treatment occurs on Thursday afternoon, when she is chatting at her girl friend's house. Later that day, Catherine also reports a low level of mQoL while sitting in the car with her boyfriend and daughter. They are having trouble finding the way to a shop. Catherine is stressed, insecure, and very irritated. In addition to dry

mouth, which she experiences most of the time, she also reports other complaints, such as dizziness and nausea. The following days show a fairly stable pattern, with Catherine's level of mQoL fluctuating between -1 and 1, very much depending on whether she is alone or with others, respectively. On Sunday, her daughter receives Holy Communion for the first time, which is reported by Catherine as a pleasant event. That evening, as she lies in bed, Catherine is concerned by the fact that she seems so calm in spite of all the excitement of the day. It makes her quite anxious. After a sleepless night, Catherine reports her lowest levels of mQoL the following day. She worries about her daughter's health (she is hyperactive), as well as her own psychic health. Her visit to the GP does not brighten her spirits much. She feels down for the rest of the day. She takes her first capsule of imipramine (50 mg) that evening.

Although complaints were already present pre-treatment, both the frequency and the severity show further increases during the first week of treatment (see Figure 4), in spite of the fact that Catherine is kept at a low dose of imipramine (50 mg, taken in the evening). Her sleep improves. She describes this as follows: 'I sleep very well and I find this great. All my problems are gone. That is a very good feeling, which I haven't felt in years.' However, her levels of mQoL gradually decrease over the three days, as she feels more and more depressed and experiences more and more nausea. Her best moment in these three days occurs while she is shopping on Saturday with her boyfriend and daughter. Her worst moment occurs early Monday morning, when she is at home alone thinking about what she has to do that day. At that moment, she describes the quality of her sleep as a positive event, but at the same time she reports the fact that she has had to get up as a negative event. During the two ESM sampling periods, Catherine spends more than 10% of her time 'doing nothing', a typical pattern for depressed patients.

DISCUSSION

The results reported here were derived from the intensive study of two cases and were meant to unravel the complexities of group-level results to obtain a better understanding of how response to treatment is translated to everyday experience.

What these two depressed women in their mid-thirties had in common was their average level of mQoL pre-treatment and the fact that they were both regarded as 'moderately ill' by their treating physician. However, based on their experiences on treatment, Suzanne was considered a responder, whereas Catherine did not adhere to the prescribed medication regimen, and was thus per definition a non-responder. As seen in Chapters 3 & 4, compliance with ESM was acceptable (above 50%) in both cases across the sampling periods, although Suzanne had a higher number of ESM self-reports in the first two periods. The cases illustrate the finding that average response time decreases over time in responders but not in non-responders to treatment. As reported

in Chapter 6 for responders, Suzanne's response to treatment over time was accompanied by an increase in average mQoL and a decrease in mQoL fluctuations, as she learns to cope with her marital problems. In contrast, Catherine's mean level of mQoL was lower in the first week of treatment than pre-treatment, even though her depressive symptoms were unchanged. As described in Chapter 6, treatment-related increases in frequency or severity of physical complaints may be associated with decrements in mQoL and lead subsequently to withdrawal. This appears to have been the case for Catherine. Both women experienced side effects, which they either did not report to their GPs, or their GPs failed to write them down. Suzanne had more frequent and more severe dry mouth as time progressed. During the last week of treatment, she actually experienced moderately severe levels of dry mouth all the time (this complaint was not present prior to treatment). Surprisingly, dry mouth was not reported as an adverse event by the GP! Catherine reported excessive transpiration and vomiting, both of moderate intensity, as adverse events to the GP. According to the ESM self-reports, Catherine experienced headache, dizziness, dry mouth, nausea and drowsiness as side effects of treatment. With the possible exception of nausea, none of these ESM side effects was reported by the GP. Even before treatment, Catherine experienced nausea half of the time, but it was mild in severity. During her week on treatment, she reported quite severe levels of nausea all of the time. Moreover, of all the side effects she experienced, nausea had the highest negative association with mQoL from moment to moment. It is possible this relationship, which cannot be established retrospectively from GP reports, may explain her non-adherence to treatment. Finally, as discussed in Chapter 5, depressed patients differ from healthy individuals in the percentage of time spent 'doing nothing'. Catherine is a good example, as she spends more than 10% of her time 'doing nothing'.

Although the causal relations identified in these two cases between treatment changes and everyday experience may well be very different in other cases, they shed light on clinically relevant differences between ESM data and traditional measures and point to the relevance of measures that should be incorporated in dynamic models of QoL. Clinicians should be made more aware of the relationship between early side effects and non-adherence, as evidenced by case 'Catherine'. Early side effects should be monitored more carefully and their impact on mQoL should be assessed thoroughly in order to better monitor treatment adherence. Clinicians should also be careful in depending on retrospective assessments of patients' QoL, as these might be biased by the most recent experience (case 'Catherine', baseline week). On the basis of the two case descriptions, it seems relevant in future daily QoL models to incorporate those negative events that are most frequently associated with low mQoL, and to determine whether the patient learns to cope with these. Furthermore, measures that are likely to contribute to a better understanding of non-adherence (e.g. attribution of side effects) should also be considered in future models of daily QoL.

These two cases illustrate how information obtained with ESM can extend understanding of how antidepressant treatment affects daily life experiences. In addition to a better insight into the changes in daily life experiences that accompany response to treatment (as in case 'Suzanne'), ESM data can also provide new information about treatment non-response, intolerance, or non-adherence (as in case 'Catherine'). In conclusion, not only does ESM yield detailed quantitative information, but the self-reports are also a rich source of qualitative description of patients' everyday experience.

REFERENCES

- Andrews, F. M., McKennell, A. C., 1980. Measures of self-reported well-being: their affective, cognitive, and other components. *Social Indicators Research* 8, 127-155.
- Hamilton, M., 1960. A rating scale for depression. *J Neurol Neurosurg Psychiat* 23, 56-62.
- Yin, R. K., 1994. Case study research. Design and methods. Second Edition. (Vol. 5). Sage Publications, Thousand Oaks, California.

PART IV DISCUSSION

CHAPTER 8 Impact of depression and antidepressant treatment in daily life: Conclusions and general discussion

Impact of depression and antidepressant treatment in daily life: Conclusions and general discussion

Major depression is both a common and a chronic condition with a high risk of suicidality. Depression imposes significant annual costs on society, not only in terms of direct costs of diagnosis and treatment, but also, and perhaps mainly in terms of lost productivity. At a micro level, the consequences of depression can dramatically affect the lives of those interacting with afflicted individuals. Studies have shown that relatives have difficulties coping with the mood disturbance of their family member because they understand so little of the impact it has in everyday activities. Depressed patients experience an inability to enjoy life. They feel impaired or unable to handle the demands of everyday life. A quantitative description of the impact of depression in daily life is required, however, for a better understanding of what it actually means to be depressed.

Since the 1950s, effective and specific pharmacological treatments, such as tricyclic drugs, have been available. Literature on RCTs in depression that include QoL assessments support the hypothesis that antidepressants, in general, enhance QoL in depressed patients as a consequence of clinical improvement. But little is known about how QoL improvements translate to changes in daily life experiences and in patterns of activities over time.

The down side of antidepressants is their side effects. In clinical trials, the determination of side effects relies upon the physician to detect signs of illness or injury that appear or worsen during treatment, and upon the patient to volunteer information to the physician. A side effects profile is then compiled on the basis of a greater percentage of patients reporting the side effect at any time on treatment than on placebo. Although this convention may work for regulatory purposes, patient and physician are found to filter and perhaps to distort information (Anderson and Testa, 1994). In addition to the unreliability of conventional assessments, they provide little insight into how side effects impinge on daily life.

The current research was intended to provide a quantitative description of the impact of depression in daily life, to clarify the changes in daily life experiences and patterns of activities that are associated with clinical improvement over time, and to investigate how side effects are experienced in daily life. For this purpose, an ecologically valid method such as ESM was needed that captures subjective experiences prospectively in real-life settings. Such a method had not been used to assess the effects of a pharmacological intervention at the outset of the current research.

CONCLUSIONS

The main conclusions of the present research can be briefly summarized with respect to the two main objectives of this thesis, as follows:

I. Feasibility and utility of ESM in clinical drug trials:

- ESM is feasible in the context of a clinical trial in depression, as a majority of depressed subjects complied with ESM and remained compliant over time (Chapters 3 & 4);
- ESM is useful in the context of a clinical trial, in that new insights on the effects of active treatment in daily life are obtained. These new insights are gained by measuring repeatedly and prospectively in real-life settings. So far, however, ESM has not been found to be quantitatively superior to conventional approaches in detecting statistically significant advantages of antidepressant treatment over placebo (Chapters 4 & 6).

II. New insights into the impact of depression and antidepressant treatment in daily life:

- Daily life experiences in depressed patients differ from that of healthy controls both in intensity and variation, even though similar daily life variables are associated with QoL changes from moment to moment (Chapter 5);
- Inactivity in daily life is a more common occurrence in depressed than in healthy individuals. The percentage of time 'doing nothing' is likely to decrease following clinical improvement (Chapters 3, 5 & 6);
- Clinical improvement in a depression trial is accompanied by changes in daily life experiences, both in quantitative estimates of time use and in emotional states occurring in daily life situations and activities (Chapters 3, 6 & 7);
- Instability in subjective well-being, a characteristic of psychiatric disorders including depression, is a temporary phenomenon that can be reduced by active treatment, independently of the level of well-being (Chapters 5, 6 & 7);
- Severity - and to a lesser extent frequency - of side effects, which are very often not reported as adverse events to the physician, are associated with decrements in levels of daily QoL during the first week of treatment. (Chapters 6 & 7).

GENERAL DISCUSSION

Application of ESM in clinical drug trials

In the present research, ESM was applied for the first time in the context of a clinical drug trial. In achieving the aim of describing the impact of depression and antidepressant treatment in daily life, ESM was found to be feasible and useful in the clinical trials context. The two clinical trials were conducted in outpatients; as over 90% of clinical trials in depression in Europe are done in outpatients¹, data on ESM compliance can thus be generalized to most studies conducted in depression in Europe. Based on the results of the two clinical studies, however, some methodological issues remain.

First, the choice of a sampling procedure requires further thought. The sampling strategy in the current research (10 times a day for 6 days) was chosen on the basis of previous experience (Delespaul, 1995). Although the sampling strategy used was effective in obtaining the maximum standardized treatment effect size for ESM measures (see Chapter 4), other sampling strategies (with fewer beeps per day) would have been more efficient in this respect. However, caution should prevail in decreasing the number of beeps per day as this could reduce the possibility of assessing within-person variability (Chapter 5).

In order to assess pre- versus post-treatment differences in the two studies, a sampling period was conducted in the baseline week and in the sixth week of treatment. In Study 2, an additional sampling period of three days was included at the end of the first week of treatment in order to study the impact of side effects in daily life. As prolongation of treatment was offered as a possibility after 6 weeks, another sampling period of 6 days was conducted in the 18th week of treatment. Ideally, sampling should have been done throughout the baseline week and the entire treatment period, but in light of the additional burden on subjects a compromise was sought between compliance and sampling requirements. However, it is possible that other sampling procedures may be better suited for obtaining insight into the improvement curve of various aspects of daily life over time or into the differential effects of treatment. For instance, in a recent application of ESM in a clinical trial, two transdermal nicotine patches were compared for relief of morning craving (Shiffman et al., 2000). ESM measures for craving (e.g. urge to smoke) were assessed between 8 and 10 times a day for 4 to 7 baseline days, while smoking *ad libitum*, and for two weeks after quitting and subsequent randomization to either a 16-hour or a 24-hour transdermal patch. ESM results showed that, besides reducing average craving intensity significantly more than the 16-hour patch, the

1 This information is obtained from Data Edge/Fast Track Systems and is based on a survey of over 140,000 grants covering all therapeutic areas.

24-hour patch cut by at least one-third the time that participants experienced craving, and reduced the frequency of temptations by 50%. Thus, the sampling strategy used by Shiffman and colleagues was effective in differentiating two types of nicotine patches. However, with only a handful of intervention studies using ESM that have been published to date, the design of optimal sampling strategies should be studied more thoroughly, possibly as an objective in itself.

In addition, with a growing number of long-term depression studies, there is a need to sample over longer periods of time. An ESM study of migraine patients, in which ESM reports were obtained 6 times a day for 10 weeks (Honkoop et al., 1999) supports the notion that continuous sampling over longer periods of time may be feasible. The finding in the current research that compliant subjects remained compliant over time (see Chapter 4) also suggests that ESM can be used with success over extended periods of time.

A second methodological consideration regards the sensitivity of ESM in a clinical trial setting. In Chapter 4, sensitivity was defined in two ways: quantitatively and qualitatively. The current focus is on the quantitative perspective; that is, can ESM reduce the number of subjects required to differentiate active treatment from placebo, when compared with conventional retrospective measures, by increasing STES? By using repeated measurements over the day and across days instead of one-time measurement, the sampling strategy used in the current research (i.e. 10 times a day for 6 days) increased STES of ESM measures, thereby increasing the likelihood of detecting true treatment differences. In Study 1, ESM once-a-day measures of sleep quality were found to be more sensitive to differences between responders and non-responders than a SIP module on sleep (see Chapter 3). In Study 2, an ESM measure (mQoL) was not found to be more sensitive than a retrospective measurement (QoL VAS) in detecting differences between imipramine and placebo (see Chapter 4). Although the variance of mQoL was, as expected, smaller than the variance of QoL VAS, the group mean difference for mQoL was, unexpectedly, also smaller. Two speculative explanations for this unexpected finding are suggested. First, the correlation between the two scales was possibly not sufficient to make such a comparison. In other words, retrospective and moment-to-moment assessments may measure intrinsically different concepts. Kahneman (Kahneman, 1999) makes a fundamental distinction between what he defines as the 'objective' (based on moment to moment states) versus the 'subjective' (evaluated retrospectively) happiness. It could be argued that both 'objective' and 'subjective' QoL (i.e., how is it experienced in real time and how is it assessed retrospectively) are important in determining the effects of treatment on patients QoL, and that future studies should investigate both aspects of QoL. Second, in the current debate on the integrity of the double-blind procedure in depression trials due to side effects (Greenberg and Fisher, 1997; Quitkin et al., 2000), some authors have suggested that

patients report enhanced improvement as a result of experiencing anticipated side effects (Antonuccio et al., 1999). As the frame of reference in ESM assessment is the description of patients' immediate emotions and behaviors, ESM may be less vulnerable to such cognitive judgmental processes and thus capture a more 'objective' (although possibly smaller) difference between treatments.

However, from the perspectives of the pharmaceutical industry and regulatory agencies, the question of whether or not ESM measures are more sensitive than retrospective measures will, in the end, determine whether ESM will be accepted in future regulatory studies as a possible substitute for primary outcome measures such as HDRS. The issue is complex. As pointed out in Chapter 2, comparisons between ESM and conventional methods are subject to discrepancies between: (1) observer-ratings versus self-ratings, (2) one-time measurement versus repeated measurement, (3) retrospective versus prospective ratings, and (4) clinical symptom versus QoL measures. Future ESM applications in depression trials should address the question of whether a relevant ESM index can be developed that is more sensitive in detecting treatment differences than commonly used primary outcome measures like the HDRS. Results of the current research suggest that such an index should consist of affective (PA, NA), cognitive-appraisal (mQoL, enjoyment of activities), and behavioral components (percentage of time doing nothing), but other aspects such as cognitive disturbances, social interactions, and coping mechanisms should also be considered. Until then, ESM should be regarded as a supplement to conventional methods in clinical trials, which can go beyond nosological and clinical perspectives to clarify the impact of treatment from an experiential perspective.

Finally, the feasibility and utility of ESM in assessing the impact of depression and anti-depressant treatment in daily life will depend on its cost-benefit ratio. Factors that should be taken into account on the cost-side of the equation include costs of the equipment used (e.g. wrist-watch, booklets) and of the data management involved; time required for training of personnel in ESM procedures as well as the time involved in briefing and debriefing sessions. On the benefit-side of the equation, new insights into personal experience of illness and recovery, not obtainable via conventional measures, should be included. Based on expected costs and benefits, future studies should evaluate the incremental costs in using ESM, either in addition to or as a substitute for conventional measures.

New insights into depression and antidepressant treatment in daily life

Burden of depression in daily life

ESM offers a supplement to the approaches taken by the numerous retrospective studies that have explored the burden of depression, in that it collects systematic data prospectively about the ongoing impact of the illness in daily life. In comparison to a control group similar in sociodemographic characteristics, depressed patients studied in the current research experienced not only lower levels of momentary QoL, but also greater variability. The burden of depression was also assessed in terms of the types of activities subjects engaged in, and the pleasure they derived from them. Results showed that depressed individuals spent a greater percentage of time doing nothing than control subjects. In addition, a greater proportion of the depressed group reported daily periods of 'doing nothing'. In spite of few other differences in time use, depressed individuals did report significantly less enjoyment than control subjects in almost all activities they engaged in. Finally, depressed individuals experienced more frequent and severe levels of physical complaints than healthy controls. Within subjects, complaints were positively associated with negative affect from moment-to-moment. It remains unclear whether the experience of complaints is a cause or a consequence of reporting negative affect, but the current results suggest that both variables make independent contributions to momentary QoL.

In general, the current research has shown that state aspects of QoL are as important as the trait-like aspects of QoL in understanding the burden of depression in daily life. Future studies investigating QoL in depression should incorporate both aspects of QoL.

Clinical improvement and daily life experiences

In the two clinical studies undertaken in the context of the present research, responders to six weeks of treatment improved more than non-responders in levels of momentary QoL and positive mood states. To a lesser extent, responders also experienced lower levels of negative mood states than non-responders. These mood differences were found across all activities, except for active leisure. In terms of time use, responders did show greater increase in productive activities, such as household chores, and greater decrease in passive leisure, such as 'doing nothing' than non-responders. Furthermore, in line with studies on self-esteem and daily events, current results showed that instability in well-being may be a marker of vulnerability to depression (see Chapter 5). At six weeks of treatment, imipramine patients, who showed a greater clinical response, experienced less variability in momentary QoL than did patients on placebo (see Chapter 6). Based on these results, it would seem that instability in well-being is more likely a temporary phenomenon than a pre-existing trait in depressed patients; instability may possibly be even more sensitive than levels of subjective well-being to drug treatment differences.

Conclusions regarding the impact of different classes of effective antidepressants are limited to the extent that few differences in daily life variables were found between different active treatments (e.g., fluvoxamine versus amitriptyline, see Chapter 3). In recent years, there is increased interest in distinguishing changes in positive and negative affect occurring as a result of antidepressant treatments. For example, pharmacological theories predict that drugs that target noradrenaline will perform better when outcome measures tap into the domain of positive affects, whereas drugs with serotonergic activity will do better on measures that assess reduction in negative affects (Healy, 1998). Another hypothesis postulates that changes in positive affect underly treatment-related changes in social activities (Lenderking et al., 1999). In the absence of a specific noradrenergic drug in the current studies, the independent roles of PA and NA could not be investigated. However, results point to independent and large effects of both PA and NA on momentary QoL. Given the salience of low PA in the phenomenology of depression, in particular (Watson et al., 1988), and the relevance of both PA and NA to the concept of well-being, in general (Diener, 1984), it is suggested that psychological models of affect in daily life should be incorporated into clinical trials more often. Inclusion of daily process models in future trials, specifically those comparing the effects of a selective serotonergic versus a selective noradrenergic drug, is expected to provide new insights into the differential effects of treatment.

The experience of side effects in daily life

Unfortunately, no currently available antidepressant is without side effects. An improved adverse event profile is considered to be one of several important targets in the search for the ideal antidepressant (DeVane, 2000). Information on the expected drug side effects profile stems from the pharmacological mode of action of the drug. However, a description of the potential side effects in the labelling is ultimately based on the data generated in a clinical trials context. Conventionally, these data are based on physician reports. Results of the current research and others (Anderson and Testa, 1994) have shown that this method of reporting may not be sufficient to obtain a good understanding of how side effects impinge on daily life, and hence, how well side effects are tolerated by patients. For this purpose, time sampling methods such as ESM are important additions to the traditional measures used in clinical trials. Dry mouth, a typical anticholinergic side effect, is a good example. The incidence of anticholinergic side effects with tricyclic antidepressant treatment usually ranges between 15% and 30% (Lader, 1983). In Study 2, however, 41.4% of imipramine-treated patients reported dry mouth to the GP (see Chapter 6). This greater percentage may have been a consequence of cueing patients on complaints with ESM, although even greater percentages have been reported in other trials without ESM (e.g. 63% imipramine-treated patients experiencing dry mouth; (Cohn et al., 1990). But what does this actually mean in the daily life of individual patients? At week 1, the average time spent with dry mouth

increased from baseline by one-third on imipramine compared to only one-tenth on placebo treatment. In addition, severity increased from baseline on average by one point (on a 7-point scale) on imipramine versus one-third of a point on placebo treatment. More importantly, an increase from baseline in either severity or frequency of dry mouth, although not reported as an adverse event by the physician, was significantly related to a decrease in average momentary QoL. A second example of how ESM offers new insights into how side effects impinge on daily life comes from the second case study in Chapter 7. Even before treatment, Catherine experienced nausea half of the time, but it was mild in severity. During her week on treatment, she reported quite severe levels of nausea all of the time. Moreover, of all the side effects she experienced, nausea had the highest negative association with momentary QoL. This relationship, which could not be established retrospectively from GP reports, may have explained her non-adherence to treatment. By providing a means to obtain more descriptive information on the experience of side effects in daily life, ESM data potentially provide a better understanding of patients' difficulties with and expectation of treatment.

A disadvantage of cueing complaints in daily life may be that a greater number of patients will report side effects more frequently. Controlling for baseline levels and including placebo arms should help to overcome these impediments. With the goal of developing safe, tolerable and effective drugs, and increasing non-adherence to drug regimens, it seems essential to enhance our understanding of how side effects are experienced in daily life, even if this occurs with methods that may increase the overall incidences of reported side effects.

Furthermore, the finding that physical complaints were still present in clinical responders at 18 weeks raises the issue of whether these are lingering side effects of treatment or a pre-existing trait, marking a certain vulnerability for depression. For many antidepressants, side effects are believed to occur mainly in the first two weeks and to disappear over time, partly due to true tolerance and partly as a result of the patient complaining less as the depression lifts (Lader, 1983). But do we really know? Long-term studies should address this question by investigating the side effects over time, both as reported by the GP and experienced by the patients in daily life.

As stated earlier, recent discussions on the reporting of typical, drug-related side effects have questioned the integrity of the double-blind in clinical trials (Antonuccio et al., 1999). In line with these concerns, current results suggested that the experience of early side effects in daily life, associated with active treatment, increased the likelihood of further prolongation of treatment (see Chapter 6). As ESM is focused on the description of the immediate personal experience, it is less likely to be affected by cognitive judgmental processes, such as taking into consideration the presence or absence of anticipated side effects. Future studies should address the role of cognitive judgmental processes (expectations and beliefs) in patients' responses.

Finally, further investigations should indicate whether the findings with respect to the experience of early side effects only hold true for conventional antidepressants such as imipramine, or also for the more specific serotonergic and noradrenergic drugs, which are believed in general to have fewer side effects.

Concluding remark

In summary, further research on the use of ESM in investigating the impact of illness and associated treatment is required. The present research focused on the impact of depression and different antidepressant treatments in daily life. Some new insights in the effects of depression and antidepressant treatment in daily life, not obtainable via conventional measures, have been gained. Daily life variables that have an independent contribution to momentary QoL have been identified. Although we have come a little further in understanding what it means in daily life to be clinically depressed and what it means in daily life to be receiving antidepressant drug treatment, much work still needs to be done in order to obtain a model of daily QoL. In this context, the role of unmeasured aspects of depression (e.g., cognitive disturbances, difficulty in coping with daily stressors) and of treatment adherence (e.g. attributions with respect to side effects) will need to be investigated in future studies. For the pharmaceutical industry, clinical trials in a broader range of disorders can assess whether ESM is a beneficial supplement to conventional approaches, as a means both of understanding the impact of drugs in daily life (early phase of development) and of differentiating drugs from competitors in terms of daily life effects (post-marketing phase).

T.S. Eliott once remarked: 'We've had the experience, but we missed the meaning'. As a general critique of conventional clinical studies in depression, we may have had the meaning, but we missed the experience.

REFERENCES

- Anderson, R. B., Testa, M. A., 1994. Symptom distress checklists as a component of quality of life measurement: comparing prompted reports by patient and physician with concurrent adverse event reports via the physician. *Drug Information Journal* 28, 89-114.
- Antonuccio, D. O., Danton, W. G., DeNelsky, G. Y., Greenberg, R. P., Gordon, J. S., 1999. Raising questions about antidepressants. *Psychother Psychosom* 68(1), 3-14.
- Cohn, J. B., Crowder, J. E., Wilcox, C. S., Ryan, P. J., 1990. A placebo- and imipramine-controlled study of paroxetine. *Psychopharmacol Bull* 26(2), 185-189.
- Delespaul, P. A. E. G., 1995. Assessing Schizophrenia in Daily Life: The Experience Sampling Method; Ph.D. dissertation, Maastricht University, Universitaire Pers, Maastricht.
- DeVane, C. L., 2000. Pharmacologic characteristics of ideal antidepressants in the 21st century. *J Clin Psychiatry* 61(Suppl 11), 4-8.
- Diener, E., 1984. Subjective well-being. *Psychological Bulletin* 95(3), 542-575.
- Greenberg, R. P., Fisher, S., 1997. Mood-mending medicines: probing drug, psychotherapy, and placebo solutions. In: Fisher, S., Greenberg, R. P. (Eds.), *From Placebo to Panacea: Putting Psychiatric Drugs to the Test*. Wiley & Sons, New York, pp. 115-172.
- Healy, D., 1998. Reboxetine, fluoxetine and social functioning as an outcome measure in antidepressant trials: implications. *Primary Care Psychiatry* 4(2), 81-89.
- Honkoop, P. C., Sorbi, M. J., Godaert, G. L., Spierings, E. L., 1999. High-density assessment of the IHS classification criteria for migraine without aura: a prospective study. *Cephalalgia* 19(4), 201-206.
- Kahneman, D., 1999. Objective happiness. In: Kahneman, D., Diener, E., Schwarz, N. (Eds.), *Well-being: the foundations of hedonic psychology*. Russell Sage Foundation, New York, pp. 3-25.
- Lader, M., 1983. The problems of safety and compliance with conventional antidepressant drugs. *Acta Psychiatr Scand Suppl* 308(5), 91-95.
- Lenderking, W. R., Tennen, H., Nackley, J. F., Hale, M. S., Turner, R. R., Testa, M. A., 1999. The effects of venlafaxine on social activity level in depressed outpatients. *J Clin Psychiatry* 60(3), 157-163.
- Quitkin, F. M., Rabkin, J. G., Gerald, J., Davis, J. M., Klein, D. F., 2000. Validity of clinical trials of antidepressants. *Am J Psychiatry* 157(3), 327-337.
- Shiffman, S., Elash, C. A., Paton, S. M., Gwaltney, C. J., Paty, J. A., Clark, D. B., Liu, K. S., Di Marino, M. E., 2000. Comparative efficacy of 24-hour and 16-hour transdermal nicotine patches for relief of morning craving. *Addiction* 95(8), 1185-1195.
- Watson, D., Clark, L. A., Carey, G., 1988. Positive and negative affectivity and their relation to anxiety and depressive disorders. *Journal of Abnormal Psychology* 97(3), 346-353.

APPENDICES

APPENDIX 1

- A. Study 1 ESM self-report beep level (Dutch)
- B. Study 1 ESM self-report beep level (English)
- C. Study 1 ESM self-report day level (Dutch)
- D. Study 1 ESM self-report day level (English)

A. STUDY 1 ESM SELF-REPORT BEEP LEVEL (DUTCH)

Wat dacht u op het moment van de piep? .... Vond u dit een prettige gedachte? ..... Was u aan het piekeren?		niet 1 2 3 4 5 6 7 1 2 3 4 5 6 7 1 2 3 4 5 6 7 1 2 3 4 5 6 7	matig 1 2 3 4 5 6 7 1 2 3 4 5 6 7 1 2 3 4 5 6 7 1 2 3 4 5 6 7	zeer 1 2 3 4 5 6 7 1 2 3 4 5 6 7 1 2 3 4 5 6 7 1 2 3 4 5 6 7
Voelde u zich op het moment van de piep: Energiek? ..... Prikkelbaar? ..... Depressief? ..... Moe? ..... Gelukkig? ..... Ontspannen? ..... Enzzaam? ..... Suf? ..... Angstig? ..... Droevig? ..... Rustig? ..... Enthousiast? ..... Boos? ..... Tevreiden?		niet 1 2 3 4 5 6 7 1 2 3 4 5 6 7 1 2 3 4 5 6 7 1 2 3 4 5 6 7 1 2 3 4 5 6 7 1 2 3 4 5 6 7 1 2 3 4 5 6 7 1 2 3 4 5 6 7 1 2 3 4 5 6 7 1 2 3 4 5 6 7 1 2 3 4 5 6 7 1 2 3 4 5 6 7 1 2 3 4 5 6 7 1 2 3 4 5 6 7	matig 1 2 3 4 5 6 7 1 2 3 4 5 6 7 1 2 3 4 5 6 7 1 2 3 4 5 6 7 1 2 3 4 5 6 7 1 2 3 4 5 6 7 1 2 3 4 5 6 7 1 2 3 4 5 6 7 1 2 3 4 5 6 7 1 2 3 4 5 6 7 1 2 3 4 5 6 7 1 2 3 4 5 6 7 1 2 3 4 5 6 7 1 2 3 4 5 6 7	zeer 1 2 3 4 5 6 7 1 2 3 4 5 6 7 1 2 3 4 5 6 7 1 2 3 4 5 6 7 1 2 3 4 5 6 7 1 2 3 4 5 6 7 1 2 3 4 5 6 7 1 2 3 4 5 6 7 1 2 3 4 5 6 7 1 2 3 4 5 6 7 1 2 3 4 5 6 7 1 2 3 4 5 6 7 1 2 3 4 5 6 7 1 2 3 4 5 6 7
Op het moment van de piep: Had u honger? ..... Had u dorst? ..... Voelde u zich gejaagd? ..... Voelde u zich slaperig? ..... Voelde u zich lekker? ..... Zo nee, waarom niet?		niet 1 2 3 4 5 6 7 1 2 3 4 5 6 7 1 2 3 4 5 6 7 1 2 3 4 5 6 7 1 2 3 4 5 6 7	matig 1 2 3 4 5 6 7 1 2 3 4 5 6 7 1 2 3 4 5 6 7 1 2 3 4 5 6 7 1 2 3 4 5 6 7	zeer 1 2 3 4 5 6 7 1 2 3 4 5 6 7 1 2 3 4 5 6 7 1 2 3 4 5 6 7 1 2 3 4 5 6 7
Waar was u op het moment van de piep? .... Was u samen met anderen? ..... NEE / JA ..... ZO JA: ..... Met hoeveel mensen was u? ..... Wie waren deze mensen? ..... Was u samen iets aan het doen? ..... Zou u liever alleen willen zijn? ..... ZO NEE: ..... Zou u liever met anderen willen zijn?				
Gebruikte u iets tussen de vorige piep en deze? Alcohol? NEE / JA, namelijk: ..... glazen Medicijnen? NEE / JA, namelijk: ..... Stoorde deze piep u? ..... Hoe laat is het nu? ..... uur ..... min				

B. STUDY 1 ESM SELF-REPORT BEEP LEVEL (ENGLISH)

What were you thinking at the moment of the beep?		At the moment of the beep:	
not at all	moderate	not at all	moderate
1 2 3 4 5 6 7	1 2 3 4 5 6 7	1 2 3 4 5 6 7	1 2 3 4 5 6 7
Was this a pleasant thought?		Were you hungry?	
Were you worrying?		Were you thirsty?	
		Did you feel agitated?	
		Did you feel sleepy?	
		Did you feel well?	
How did you feel at the moment of the beep:		Between the previous beep and this one, did you use ...	
not at all	moderate	not at all	moderate
1 2 3 4 5 6 7	1 2 3 4 5 6 7	1 2 3 4 5 6 7	1 2 3 4 5 6 7
Energetic?		Alcohol? NO / YES, amount:	
Irritable?		Medication? NO / YES, type and dose:	
Depressed?		Did the beep disturb you?	
Tired?		What time is it now? ..... hr ..... min	
Happy?			
Relaxed?			
Lonely?			
Drowsy?			
Anxious?			
Sad?			
Calm?			
Enthusiastic?			
Angry?			
Satisfied?			
What were you doing at the time of the beep?		What were you doing at the time of the beep?	
not at all	moderate	not at all	moderate
1 2 3 4 5 6 7	1 2 3 4 5 6 7	1 2 3 4 5 6 7	1 2 3 4 5 6 7
Were you enjoying it?		Were you doing any physical activity?	
Was it difficult for you?		Examples: 1=lying 2=sitting 3=walking 4=cleaning 5=biking 6=playing tennis 7=jogging	
Could you keep your thoughts on it?			
Would you have rather done something else?			

C. STUDY 1 ESM SELF-REPORT DAY LEVEL (DUTCH)

Goedemorgen,

Beantwoord de volgende vragen wanneer u opstaat en het horloge weer heeft aangezet:

Datum: / /

Hoe laat ging u gisteravond naar bed? uur min

Hoe lang duurde het voor u insliep gisteravond? uur min

Hoe vaak werd u in de afgelopen nacht wakker? keer

Hoe lang lag u vanochtend wakker voordat u opstond? min

Hoe laat is het nu (tijd van opstaan)? uur min

Hoe heeft u vannacht geslapen? zeer slecht matig zeer goed
1 2 3 4 5 6 7

Opmerkingen:

Beantwoord de volgende vragen net voor u gaat slapen:

Heeft u het horloge vandaag nog uitgezet? Nee / Ja

Zo ja, wanneer en waarom?

Van: uur min tot: uur min

Reden:

Van: uur min tot: uur min

Reden:

Vond u dit een gewone dag? niet matig zeer
1 2 3 4 5 6 7

Zou u zonder de pleier andere dingen
vandaag hebben gedaan? 1 2 3 4 5 6 7

Had het onderzoek een invloed op
uw stemming 1 2 3 4 5 6 7

Heeft u vanmorgen ontbeten? Nee / Ja, om: uur min

Heeft u vanmiddag gegeten? Nee / Ja, om: uur min

Heeft u vanavond gegeten? Nee / Ja, om: uur min

Bent u naar uw werk gegaan? Nee / Ja, van: uur min
tot: uur min

Hoe laat is het nu? uur min Slaap lekker!

D. STUDY 1 ESM SELF-REPORT DAY LEVEL (ENGLISH)

Good morning,

Please answer the following questions when you get up and put on your watch:

Date: ..... / ..... / .....

At what time did you go to bed last night?   hr ..... min .....

How long did it take you to fall asleep?

How often did you wake up during the night? .....

How long were you awake before getting up this morning? _____ min

What time is it now (getting up time)?

How was your sleep?

Remarks:

[illegible]

Please answer the following questions just before going to bed:

Did you turn off the watch signal today?

If yes, when and why?

From: ..... hr ..... min to: ..... hr ..... min

Reason: .....

From: _____ hr _____ min to: _____ hr _____ min

Reason:

Was this an ordinary day?	not at all	moderate	very
	1	2	3
	4	5	6
	7		

Without the beeper, would you have done other activities today?

Did the study procedure influence your mood?

Did you have breakfast today? No / Yes, at: ..... hr ..... min

Did you have lunch today? No / Yes, at: _____ hr _____ min

Did you have dinner today? No / Yes, at: hr min

Did you go to work today?

unit.
hr

What time is it now?   hr   min   Sleep well!

doi:10.1371/journal.pone.0141404.g001

APPENDICES

APPENDIX 2

- A. Study 2 ESM self-report beep level (Dutch)
- B. Study 2 ESM self-report beep level (English)
- C. Study 2 ESM self-report day level (Dutch)
- D. Study 2 ESM self-report day level (English)

A. STUDY 2 ESM SELF-REPORT BEEP LEVEL (DUTCH)

Op het moment van de piep:		zeer slecht		zeer goed	
Globaal gezien, hoe gaat het met u?		-3	-2	-1	0 1 2 3
Kan u zich concentreren?		niet	'n beetje	nogal	zeer
Bent u aan het piekeren?		1	2	3	4 5 6 7
Zo ja, waarover:		1	2	3	4 5 6 7

Voelt u zich:		niet		'n beetje		nogal		zeer	
- Vrijdij?		1	2	3	4	5	6	7	
- Energiek?		1	2	3	4	5	6	7	
- Depressief?		1	2	3	4	5	6	7	
- Opgewekt?		1	2	3	4	5	6	7	
- Gespannen?		1	2	3	4	5	6	7	
- Tevreden?		1	2	3	4	5	6	7	
- Alert?		1	2	3	4	5	6	7	
- Enzaam?		1	2	3	4	5	6	7	
- Moe?		1	2	3	4	5	6	7	
- Angstig?		1	2	3	4	5	6	7	
- Kalm?		1	2	3	4	5	6	7	
- Onzeker?		1	2	3	4	5	6	7	
- Schuldig?		1	2	3	4	5	6	7	
- Enthousiast?		1	2	3	4	5	6	7	
- Opgejaagd?		1	2	3	4	5	6	7	
- Sterk?		1	2	3	4	5	6	7	
- Gelukkig?		1	2	3	4	5	6	7	
- Prikkelbaar?		1	2	3	4	5	6	7	

Wat bent u aan het doen?		niet		'n beetje		nogal		zeer	
Doet u het graag?		1	2	3	4	5	6	7	
Kosten het u moeite?		1	2	3	4	5	6	7	
Kan u het goed?		1	2	3	4	5	6	7	
Is het een uitdaging voor u?		1	2	3	4	5	6	7	

Waar bent u?	Nee / Ja, met		mensen	
Bent u samen met anderen?	niet	'n beetje	nogal	zeer
Zo ja, met wie?	1	2	3	4 5 6 7
Bent u samen iets aan het doen?	niet	'n beetje	nogal	zeer
Zou u liever alleen willen zijn?	1	2	3	4 5 6 7

Heeft u nu last van:	niet		'n beetje		nogal		zeer	
- Hoofdpijn?	1	2	3	4	5	6	7	
- Duizeligheid?	1	2	3	4	5	6	7	
- Droge mond?	1	2	3	4	5	6	7	
- Misselijkheid?	1	2	3	4	5	6	7	
- Sufheid?	1	2	3	4	5	6	7	
- Anderen, nl.:	1	2	3	4	5	6	7	

Was er tussen deze en de vorige piep sprake van:		Nee / Ja	
Een positieve gebeurtenis of situatie:			
Zo ja, geef een korte omschrijving:			
Hoe plezierig was dit voor u?		niet	'n beetje
		1	2 3 4 5 6 7

Was er tussen deze en de vorige piep sprake van:		Nee / Ja	
Een negatieve gebeurtenis of situatie:			
Zo ja, geef een korte omschrijving:			
Hoe vervelend was dit voor u?		niet	'n beetje
		1	2 3 4 5 6 7

Stoorde deze piep u?		niet	'n beetje	nogal	zeer
		1	2	3	4 5 6 7
Hoe laat is het nu?		uur		min	
Niet invullen a.u.b.		PIEP: <u> </u>			

C. STUDY 2 ESM SELF-REPORT DAY LEVEL (DUTCH)

Beantwoord de volgende vragen net voor u gaat slapen:

Heeft u het horloge vandaag nog uitgezet? Nee / Ja

Zo ja, wanneer en waarom?

Van: ..... uur ..... min tot: ..... uur ..... min

Reden: .....

Van: ..... uur ..... min tot: ..... uur ..... min

Reden: .....

Van: ..... uur ..... min tot: ..... uur ..... min

Reden: .....

Vond u dit een gewone dag?

Had het onderzoek een invloed op:

- uw stemming?

- uw gedachten?

- uw activiteiten?

Heeft u vanmorgen ontbeten? Nee / Ja, om: ..... uur ..... min

Heeft u vanmiddag gegeten? Nee / Ja, om: ..... uur ..... min

Heeft u vanavond gegeten? Nee / Ja, om: ..... uur ..... min

Bent u naar uw werk gegaan? Nee / Ja, van: ..... uur ..... min

tot: ..... uur ..... min

Hoe laat is het nu? ..... uur ..... min Slaap lekker!

Goedemorgen,

Beantwoord graag de volgende vragen wanneer u opstaat en het horloge weer heeft aangezet:

Datum: ..... / ..... / .....

Hoe laat ging u gisteravond naar bed? ..... uur ..... min

Hoe lang duurde het voor u insliep? ..... uur ..... min

Hoe vaak werd u in de afgelopen nacht wakker? ..... keer

Hoe lang lag u vanochtend wakker voordat u opstond? ..... min

Hoe laat bent u opgestaan? ..... uur ..... min

Hoe goed heeft u vannacht geslapen?

niet 'n beetje nogal zeer

1 2 3 4 5 6 7

Opmerkingen:

.....

.....

.....

.....

.....

.....

D. STUDY 2 ESM SELF-REPORT DAY LEVEL (ENGLISH)

Please answer the following questions just before going to bed:

Did you turn off the watch signal today? No / Yes
If yes, when and why?
From: ..... hr ..... min to: ..... hr ..... min

Reason: .....

From: ..... hr ..... min to: ..... hr ..... min

Reason: .....

From: ..... hr ..... min to: ..... hr ..... min

Reason: .....

	not at all			a little			rather			very		
	1	2	3	4	5	6	7					
Was this an ordinary day?												
Did the study procedure have an influence on:												
- your mood?	1	2	3	4	5	6	7					
- your thoughts?	1	2	3	4	5	6	7					
- your activities?	1	2	3	4	5	6	7					

Did you have breakfast today? No / Yes, at: ..... hr ..... min

Did you have lunch today? No / Yes, at: ..... hr ..... min

Did you have dinner today? No / Yes, at: ..... hr ..... min

Did you go to work today? No / Yes, from: ..... hr ..... min

until: ..... hr ..... min

What time is it now? ..... hr ..... min Sleep well!

Good morning,

Please answer the following questions when you get up and put on your watch:

Date: ..... / ..... / .....

At what time did you go to bed last night? ..... hr ..... min

How long did it take you to fall asleep? ..... hr ..... min

How often did you wake up during the night? ..... time(s)

How long were you awake before getting up this morning? ..... min

At what time did you get up? ..... hr ..... min

	not at all			a little			rather			very		
	1	2	3	4	5	6	7					
How well did you sleep?												

Remarks:

.....

.....

.....

.....

.....

.....

.....

Summary

This thesis explores the effects of depression as well as of antidepressant treatment in daily life. In Chapter 1, the burden of depression is described and treatment issues surrounding antidepressants are outlined. Furthermore, the introduction of the Quality of Life (QoL) concept in clinical research is reviewed. In light of the limitations of the currently used QoL instruments in depression, Chapter 2 describes the Experience Sampling Method (ESM) as a way to investigate the impact of depression and the effects of antidepressant treatment prospectively in real life settings. Chapter 3 presents the results of Study 1, a first exploration of the use of ESM in a clinical trial context. Here, a sample of 21 depressed patients who were randomized to either fluvoxamine or amitriptyline treatment (single-blind) for 6 weeks, completed ESM booklets for 6 days pre-treatment and again for 6 days in the last week of treatment. Compliance with ESM was good in both sampling periods, with 81% of self-reports responded to within 15 min. On a retrospective generic QoL measure (Sickness Impact Profile), clinical responders were found to improve relative to non-responders in the domains of household chores, leisure and social activities. ESM results further clarified the improvement in these three areas of life with: (1) responders increasing time spent on chores and reducing time spent on passive leisure, (2) responders experiencing greater changes in average mood states across the life domains than non-responders, and (3) responders reporting highly positive mood states more often than non-responders. The next four chapters describe results obtained in Study 2. In this study, 63 patients were randomized to either imipramine or placebo, which they received (double-blind) for 6 weeks, with a possible prolongation to 18 weeks. A control group of 22 healthy individuals provided normative data. ESM was conducted pre-treatment, and in the 1st, 6th, and 18th week of treatment. Chapter 4 addresses a number of methodological issues concerning the feasibility and the utility of using ESM in depression and in a clinical trial. It appeared that depressed patients complied with ESM over time as well as healthy individuals, despite more initial difficulty and disturbance. The results further suggested that patients were able to provide a valid and reliable representation of their daily lives with ESM. By using repeated measurements over the day and across days instead of one-time measurement, the current sampling strategy (i.e. 10 times a day for 6 days) increased the standardized treatment effect size (STES) of ESM measures, thereby increasing the likelihood of detecting true treatment differences. Although the sampling strategy used was effective in obtaining the maximum STES for ESM measures, other sampling strategies (with a lower number of beeps per day) may be more efficient in this respect. Surprisingly, ESM measures were not found to be more sensitive than

conceptually related retrospective measures in detecting differences between drug and placebo. Two speculative explanations are proposed. Chapter 5 uses ESM data to investigate differences between depressed and control groups. Depressed subjects reported lower levels in positive mood and enjoyment of activity, higher negative mood, and more frequent and severe complaints than the healthy individuals. In addition, depressed subjects were more likely than control subjects to be doing nothing and less likely to be engaged in work. Moreover, moment to moment QoL (mQoL) in depressed subjects was found to be lower and more variable within the day than in controls. Multilevel regression analysis showed that mQoL was more influenced by transient states and daily experiences than a conceptually related retrospective measure, underscoring the potential value of the ESM approach as a tool in understanding changes in QoL during the course of antidepressant treatment. This aspect is investigated in Chapter 6. Results showed that treatment-related increases in frequency or severity of physical complaints, including those not reported to the general practitioner as side effects, were associated with decrements in mQoL, which may have led to subsequent treatment drop-out. Results further indicated that six weeks of imipramine treatment had a stronger stabilizing effect on mQoL than placebo treatment. Changes in measures of daily functioning (i.e. time spent doing nothing) were also observed after six weeks. However, at 18 weeks, the majority of patients, including those who responded to treatment, still showed deficits on daily life measures relative to healthy controls; even though QoL had returned to normal on retrospective measures. In Chapter 7, two case examples are presented to illustrate the quantitative findings of Chapters 4, 5 and 6. The case of Suzanne, a responder to imipramine treatment, demonstrates the value of ESM in providing better insight into changes in daily life experiences that accompany treatment response. The case of Catherine illustrates ESM as a means for obtaining a better understanding of non-response, drug intolerance, or non-adherence. Chapter 8 summarizes the main findings of the two studies and discusses them in terms of the application of ESM in clinical drug trials and the new insights, obtained via ESM, into the burden of depression in daily life, clinical improvement and daily life experiences, and the experiences of side effects in daily life. Implications for practice and future research are suggested.

Samenvatting

Dit proefschrift onderzoekt de gevolgen van een depressie en de effecten van het gebruik van antidepressiva op het dagelijks leven. In Hoofdstuk 1 worden de negatieve gevolgen van een depressie en problemen die verband houden met het gebruik van de huidige antidepressiva in hoofdlijnen beschreven. Vervolgens wordt er een overzicht gegeven van de introductie van het begrip 'Kwaliteit van Leven' (Quality of Life, QoL) in het klinisch onderzoek. In het licht van de beperkingen van de huidige gebruikte QoL instrumenten bij depressie onderzoek geeft Hoofdstuk 2 een beschrijving van de Experience Sampling Method (ESM). ESM is een onderzoeksmethode waarmee het mogelijk is om prospectief en op basis van herhaalde observaties de invloed van depressie en de effecten van antidepressiva te meten in de natuurlijke omgeving. In Hoofdstuk 3 worden de resultaten van de eerste toepassing van ESM in een klinische studie (Studie 1) gepresenteerd. In deze studie hebben 21 depressieve patiënten, die gedurende 6 weken fluvoxamine of amitriptyline voorgeschreven kregen, 6 dagen ESM boekjes ingevuld vóór behandeling en nog eens 6 dagen in de laatste week van de behandeling. Tijdens beide periodes werden de boekjes goed ingevuld; 81% van alle vragenlijsten werd binnen 15 minuten ingevuld. Gemeten met een retrospectieve generische QoL-maat (Sickness Impact Profile) verbeterde de toestand van de mensen die positief reageerden op de behandeling (responders) zich meer dan de mensen die niet of nauwelijks reageerden (non-responders) op het gebied van huishoudelijke taken, vrijetijdsbesteding en sociale activiteiten. ESM-resultaten verhelderden deze bevindingen doordat: (1) responders meer tijd gingen besteden aan huishoudelijke activiteiten en minder aan passieve vrijetijdsbestedingen, (2) responders een grotere verbetering in hun stemming constateerden gedurende de diverse activiteiten dan non-responders, en (3) responders frequenter dan non-responders momenten van extreem positieve stemming rapporteerden. De volgende vier hoofdstukken (Hoofdstuk 4, 5, 6 en 7) beschrijven de resultaten die verkregen zijn in Studie 2. In deze studie hebben 63 patiënten op aselecte wijze het antidepressivum imipramine of placebo voorgeschreven gekregen gedurende 6 weken (dubbel-blind), met een mogelijke verlenging tot 18 weken. Tweeëntwintig gezonde individuen zorgden voor normatieve gegevens. ESM werd uitgevoerd in de week voorafgaand aan de behandeling en in de eerste, zesde en achttiende week van de behandeling. Hoofdstuk 4 behandelt verscheidene methodologische kwesties die betrekking hebben op de uitvoerbaarheid en het nut van ESM in een klinisch onderzoek naar depressie. Depressieve patiënten voldeden even goed als gezonde vrijwilligers aan ESM ondanks het feit dat ze in het begin meer moeite en storing ondervonden. Verder lieten de resultaten zien dat

patiënten in staat waren een valide en representatief beeld te geven van hun dagelijks leven met behulp van ESM. Door herhaaldelijke metingen gedurende de dag en over een periode van meerdere dagen verhoogde de huidige ESM-sampling strategie (te weten tien keer per dag gedurende zes dagen) de genormaliseerde effectgrootte (standardized treatment effect size, STES) van de ESM maten, waardoor de kans op het vinden van een echt behandelingsverschil vergroot werd. Alhoewel de gebruikte sampling strategie effectief bleek in het verkrijgen van een maximum STES voor de ESM maten, zou het toch mogelijk kunnen zijn dat andere sampling strategieën nog efficiënter blijken. Tegen de verwachting in bleken ESM maten niet gevoeliger te zijn voor verschillen tussen actief (imipramine) en placebo dan conceptueel gerelateerde retrospectieve maten. Op zoek naar een oorzaak worden twee speculatieve verklaringen gegeven. Hoofdstuk 5 maakt gebruik van de ESM-gegevens om verschillen tussen de depressieve en de controlegroep te onderzoeken. Depressieve patiënten rapporteerden een lagere positieve stemming, minder plezier in de activiteiten die zij ondernamen, een hogere negatieve stemming en tevens frequentere en ernstiger klachten dan gezonde mensen. Verder bleken depressieve patiënten minder vaak dan gezonde mensen te werken en vaker inactief te zijn. Bovendien, was de kwaliteit van leven van moment tot moment (gedefinieerd als mQoL) lager en meer variabel gedurende de dag dan bij gezonde mensen. Een multilevel regressie-analyse bracht aan het licht dat mQoL meer beïnvloed wordt door kortdurende momenten en dagelijkse ervaringen dan een conceptueel gerelateerde retrospectieve maat. Hiermee wordt de potentiële waarde van ESM belicht om een beter inzicht te krijgen in veranderingen in QoL die optreden gedurende een behandeling met antidepressiva. Deze veranderingen worden verder onderzocht in Hoofdstuk 6. De resultaten (van het onderzoek) lieten zien dat een verhoging in de frequentie of de ernst van klachten, waaronder ook die klachten die niet als bijwerking aan de arts gerapporteerd waren, geassocieerd was met een vermindering van mQoL, hetgeen geleid kan hebben tot vervroegde beëindiging van deelname aan het onderzoek. Verder bleek bij de meting na 6 weken dat imipramine een sterker stabiliserend effect had op mQoL dan het placebo. Veranderingen in het dagelijks functioneren (met name de tijd besteed aan het inactief zijn) werden ook na 6 weken waargenomen. Echter na 18 weken behandeling bleek de meerderheid van de patiënten, ook diegenen die een goede respons hadden vertoond, er op basis van ESM in het dagelijks leven nog steeds slechter aan toe te zijn dan gezonde mensen, terwijl dit op basis van retrospectieve maten niet langer het geval bleek te zijn. In Hoofdstuk 7 worden twee casus gepresenteerd om de kwantitatieve bevindingen uit de hoofdstukken 4, 5 en 6 te illustreren. De casus 'Suzanne', die een goede respons heeft op de behandeling, laat zien dat ESM een mogelijkheid biedt om een beter inzicht te krijgen in de veranderingen die zich voordoen in het dagelijks leven als gevolg van een goede respons. De casus 'Catherine' illustreert ESM als een manier om een beter inzicht te krijgen in gevallen waar een respons uitblijft, het geneesmiddel niet wordt verdragen,

of er sprake is van onvoldoende therapietrouw. Hoofdstuk 8 vat de belangrijkste bevindingen samen en bespreekt deze ten aanzien van de toepassing van ESM in klinische studies en ten aanzien van de - door middel van ESM - nieuw verkregen inzichten in de gevolgen van depressie voor het dagelijks leven, de klinische verbetering en de daarmee gepaard gaande dagelijkse ervaringen en tenslotte de invloed van de bijwerkingen van antidepressiva op het dagelijkse leven. Gevolgen voor de praktijk en suggesties voor toekomstig onderzoek komen eveneens aan de orde.

Acknowledgments

A 'Dissociative Identity Disorder', better known as a 'Split-type Personality Disorder' is characterized by the presence of two distinct personality states in one individual, which are perceived by the individual's environment. Working in two distinct locations, both geographically (Amsterdam/Maastricht) and functionally (industry/academia) can be compared to a 'Dissociative Identity Disorder', which is only perceived by the individual concerned. There are many people I am indebted to for the fact that this disorder has never become applicable to me.

First of all I thank Dr. Roland Gerritsen van der Hoop. The idea of doing this research was born on our way back by train from a work visit to the Department of Psychiatry and Neuropsychology in Maastricht in June 1991. Thanks to his infectious enthusiasm, he helped rally support for the project within Solvay Pharmaceuticals. Since then, even after he was appointed to Solvay Pharmaceuticals in the USA, Roland has continued to remain involved with the project by providing helpful comments on the various manuscripts.

Professor Marten deVries has helped me broaden my scientific horizon by his never-ending, stimulating thoughts and his multidisciplinary approach. Although initially I was not always able to appreciate the value of Marten's original ideas, I have actually come to miss the challenging discussions as they became less frequent over the years. I would like to acknowledge Marten's flexibility in accepting an 'honorary OIO' (as he himself put it), who would always place her work for Solvay Pharmaceuticals as her first priority over her thesis.

I could never have managed without the extensive and highly qualified support of Dr. Nancy Nicolson. I thank Nancy for the innumerable hours she has spent on my project, the countless comments she has provided on my manuscripts, and the invaluable scientific knowledge she has imparted to me. In view of the time constraints we always experienced, our discussions were to the point and efficient, thereby even allowing some time to keep track of each other personally. In short, I experienced that as inspiring teamwork!

Over the years, I have been able to exchange thoughts with many of my colleagues in Maastricht. In this context, I mention Dr. Philippe Delespaul, a sincere person, who was always there for me and who gave me great deal of support in setting-up and imple-

menting the ESM studies. Dr. Hans Berkhof provided inestimable statistical input when it came to hierarchical linear models. I am grateful to Truda Driesen and Frieda Delespaul-Goethem for helping me become acquainted with the practical aspects of the Experience Sampling Method and for their diligence in coding and entering the data. Furthermore, I thank the secretaries from the Department, especially Trees Soure, who made it possible to conduct this research project from such a distance.

My gratitude goes to Solvay Pharmaceuticals, for having provided me the opportunity of carrying out my research project. In this context, I thank Marianne Mak for her critical concerns about my personal well-being. Jos Nauta's advice and involvement in Chapter 4 in particular and his willingness to discuss thorny issues have strengthened me in my conviction that no sound research can be done without statisticians. At the same time, I acknowledge the help that Jeroen Tolboom and Frank Kok gave with specific statistical calculations. It is a good thing that I have not kept track of all the literature requests I have made over the years. I realize they presented a lot of work to my ex-colleagues from BWI and thank them for it. Especially Rob van Spronsen made it his personal responsibility to ensure that the availability of the articles would not become a rate-limiting step in my research. Finally, I thank all my ex-colleagues, with whom I have enjoyed working over the years, for their understanding of my 'double' life.

I am indebted to the depressed patients and healthy volunteers, who took part in the two clinical trials, that have provided the data for this dissertation. The studies could not have taken place without the well-organized group of general practitioners, i.e. M.F.J. Bemelmans, R.H.J. Brouwers, G. Costongs, A.C.J. Schlösser, J.J.M. Theunissen, P.G.J. van Aubel, D.J.M. van der Voort, and M. Weijts, and their incredibly motivated research assistants, Loes Stokkermans, Pauline Versteeg, and Toos van der Voort.

Furthermore, I gratefully acknowledge Agnès Charlemagne for the graphical design on the cover, which is her personal reflection of the contents of this thesis.

In the summer of 1992, I spent time in Maastricht to become acquainted with the Experience Sampling Method. During this time, I stayed with Désirée Brenninkmeijer and her children. I gratefully appreciate how they introduced me to the 'Mestreechse' way of life.

In choosing Francine Donnelly-Verhoeff as my 'paranimf', I thank all my dear friends, who have kept confidence in me over the years. Through her ability to finalize her thesis under more penurious circumstances, Francine has set an example for me.

My other 'paranimf' is Benedikte Bruijs-Schaapveld, in whom I thank all my brothers, sisters, and in-laws for their support and encouragement, but also for helping me

keep my feet on the ground. Benedikte convinced me to opt for a sabbatical leave in order to finalize this thesis. I thank her for persuading me.

Two individuals have kept me going over the years. First of all Radboud Schaapveld, who would have been the first in the family to obtain his doctor's degree and would have pointed this out to me, if he were still amongst us. And second, Professor Jan Nauta, or rather 'oom' Jan, who pictured the development of a Ph.D. thesis as such a nightmare that the reality was actually a pleasant surprise.

I thank my parents for all the time, patience and effort they have put into my education, and all the opportunities they gave me. In this context, I thank them especially for the high level of self-discipline, which they helped me acquire. Furthermore, I am grateful to Leticia Paraiso-Alencar for her flexibility in taking care of Ludovic and Céline. Without her, Frederic and I would not have been able to develop our professional careers over the past 5 years. Finally, I am deeply indebted to Frederic for his unconditional love and support throughout the 'double' life I have led since 1993. He also made me realize that a master's degree in information management does not say anything about the person's ability to work on a computer!

Amsterdam, 2001

Daniela Q.C.M. Barge-Schaapveld

Curriculum vitae

Daniela Quirina Carola Maria Barge-Schaapveld was born on July 23, 1966, in New York (USA). She followed her secondary education (Baccalauréat C) at the Lycée Français de Londres in London (UK), via the Cours par Correspondance from Brasilia (Brazil), and finally at the Ecole Française de La Haye in The Hague (The Netherlands). In 1983, she started a degree in medical information management at the University of Leiden (The Netherlands), which she completed in 1989. She was subsequently employed by Solvay Pharmaceuticals (previously Duphar), where she worked for 11 years in clinical research and international marketing. As a Clinical Research Director, she was responsible for the clinical development of psychopharmacologic drugs. She has been affiliated with the Department of Psychiatry and Neuropsychology at Maastricht University (The Netherlands) since 1993, conducting her dissertation research with financial and logistical support from Solvay Pharmaceuticals. In 1994, she obtained a 'propedeuse' in psychology at the University of Amsterdam (The Netherlands). In 1995/1996, she completed requirements for the European Certificate in Anxiety & Mood Disorders (Erasmus Programme, Maastricht/Caen).