

# Hyperarousal in the hospital and what to do about it

Citation for published version (APA):

Leue, C. (2017). *Hyperarousal in the hospital and what to do about it: the MED-PSYCH-NET - a transitional network approach fostering personalized care in psychosomatic medicine*. [Doctoral Thesis, Maastricht University]. Datawyse / Universitaire Pers Maastricht. <https://doi.org/10.26481/dis.20171214cl>

## Document status and date:

Published: 01/01/2017

## DOI:

[10.26481/dis.20171214cl](https://doi.org/10.26481/dis.20171214cl)

## 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](http://www.umlib.nl/taverne-license)

## Take down policy

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

[repository@maastrichtuniversity.nl](mailto:repository@maastrichtuniversity.nl)

providing details and we will investigate your claim.

the other hand, the scientific understanding of multi-conditional pathways may profit from ESM-data too, especially if the course of complex symptoms in relation to treatment can be combined with repeatedly measured biomarkers or epigenetic changes. Eventually, ESM may serve as a reliable patient-related outcome measurement (PROM) tool, which may prepare the ground for reimbursement changes in the future, i.e., payment for performance instead of payment for service, that might help to overcome the current reimbursement dichotomy between soma and psyche

chapter15,342,361

## Valorisation

This PhD thesis presents a series of studies and articles with diverse objectives: i) to investigate and describe the effect of psychosomatic integrated care on complex (functional) conditions at various clinical levels; ii) to develop an integrated transitional care model, i.e., the Med-Psych-Net, that enables care givers to accompany multi-conditional patients from the hospital to primary care and vice versa, in order to overcome the disadvantages of mono-disciplinary trajectories; iii) to conceptualize a system-based etiologic nosology of complex (functional) syndromes; and iv) to introduce a modern m-health tool, the ESM, that may advance the development of tailored personalized medicine, clinical reasoning and the scientific understanding of pleiotropic multi-morbidity.

This valorisation section places the outcomes of this thesis in a broader societal context in order to address how this transitional Med-Psych-Net may be further implemented in daily clinical practice. Its societal importance will be considered from three perspectives: 1) the relevance of scientific findings for clinical practice; 2) the clinical target groups to whom the findings are relevant; and 3) the translation of the findings into Med-Psych-Net activities concerning innovativeness, feasibility, implementation and perspectives for future research.

## Relevance

Functional somatic disorders as well as mental disorders are highly prevalent<sup>362-364</sup>. Data from epidemiological studies indicate that depression and anxiety disorders as well as, for instance, functional urological and related gastrointestinal disorders are common comorbidities having adverse effects on patients' outcomes<sup>59,88,286,287,290,313,365-367</sup>. Moreover, the common association between functional urological and gastrointestinal disorders affects the severity of experienced physical and mental symptoms in a dose-dependent fashion<sup>236-242,287,368,369</sup>. Additionally, the prevalence of anxiety disorders and depression increases with the number of functional disorders and the frequency or severity of functional somatic symptoms<sup>284,288,312,313,315,370</sup>. Thus, the more severe the

somatic symptoms are, the more prevalent the affective complaints become. Pain and depression are closely associated<sup>281,282,284-287,307,310,312</sup>. Affective complaints might therefore complicate or amplify existing functional complaints, and the onset of anxiety and depressive symptoms might precede that of, for example, urological functional disorders<sup>59,371,372</sup>. Similarly, depression and anxiety both dose-dependently increase the risk of developing urinary incontinence, and the number of neuroticism-associated conditions (i.e., functional as well as affective disorders) might be a marker of a complex psychosomatic multi-morbidity phenotype<sup>239,281,285,295,313,373,374</sup>. Thus, in cases of (functional) clinical complexity, psychiatric comorbidity has to be taken into account in order to avoid misdiagnosis and treatment resistance. However, in the medical hospital, where complex cases will present themselves at a certain point in a patient's career, clinical complexity, including psychiatric comorbidity, is frequently under-detected. For example, at the emergency department, in the outpatient medical hospital setting and in clinical general hospital wards, affective comorbidities frequently go undetected, which has an impact on care utilization later on<sup>17,20,43</sup>. This also applies to the most complex and severely ill patients in the intensive care unit (ICU), where psychiatric case detection concerning transitional care for delirium, which is traditionally considered organic and not functional, still deserves attention<sup>375</sup>.

Multi-morbidity and the characteristics of health care providers are predictors for complications of hospital interventions. Therefore, the length of hospital stay and the rate of unplanned hospital readmission are the main medical cost factors in complexity care that need to be kept in mind with regard to reducing the societal cost of care at the hospital level<sup>20,376-380</sup>. The need for this focus has become more and more obvious; the percentage of hospital stays for multi-conditional patients increased between 2003 and 2014 in the US from approximately 65% to 80%, whereas hospital stays for adults without multi-conditional complaints decreased from roughly 35% to 20% during the same period<sup>381</sup>. Moreover, given that hospital stays for adult patients with multiple conditions cost on average 20% more than stays for inpatients with a mono-conditional background, it would seem quite reasonable to pursue enhanced integrated hospital and transitional care from a hospital cost perspective<sup>381</sup>. Furthermore, integrated care has to incorporate psychosomatic complexity, as almost one-third of inpatient hospital stays in the US involved mental disorders in 2012, whereby affective disorders were the most common mental disorder diagnoses<sup>379</sup>. Comparable trends have been noted for unplanned readmissions in the US: readmission rates increased substantially between 2009 and 2013, and their average cost was higher than the average cost of index admissions<sup>382</sup>. This is also true for readmissions involving mood disorders compared with initial hospital stays<sup>383</sup>. Thus, hospital readmissions within 30 days of discharge represent a negative clinical outcome. They might be due to a lack of integrated hospital care solutions and poor access to adequate primary or community-based aftercare. Clearly, transitional integrated approaches concerning multi-morbidity in complex psychosomatic syndromes face a challenge<sup>156,384,385</sup>. The level of comorbidity care and the

quality of illness management across settings are very relevant to attempts to avoid every kind of hospital readmission<sup>386-388</sup>. This consideration is indirectly supported by our own hospital evaluations (MUMC) concerning wards which are still running without a transitional network approach, especially without routinely integrated psychosomatic care for patients with a high chance of medical and psychiatric comorbidities<sup>174,175</sup>.

## Target groups

Besides complex multi-conditional patients, health care providers from in- and outside the general hospital and the patients' environment (i.e., family and social network) are important target groups for integrated transitional care in psychosomatic medicine. From our clinical experience, patient and social network empowerment due to a "warm handover" across settings by case managers as well as the availability of medical skills guaranteed by integrated medical staff-guidance are essential. Transitional care by case managers can be effectively realized by medical staff-guided care givers from outside the MUMC, as suggested by our investigation<sup>chapter7</sup>, or instead by multi-disciplinarily guided care managers related to general hospital-based disease management programmes. Primary care-based collaborative care is very well suited to long-distance communication between care givers and patients in rural areas. But the Med-Psych-Net approach may be especially productive in urban areas, where complex patients accumulate at the hospital level and where GPs as well as mono-disciplinary general hospital-related treatment options might fail. Depending on the severity and complexity of patients' multi-conditional complaints, the Med-Psych-Net approach would start in the ICU setting, for example, in multi-disciplinary delirium care (i.e., proactive CLS involving integrated multi-disciplinary medical staff-guidance and transitional case management by nurse practitioners), or at the MPU and at medical wards for comorbidity care. Most importantly, all clinical settings require guided CM in order to accompany inpatients from care at a higher to a lower level of complexity, depending on the patients' state of clinical severity. In complex but less severe multi-conditional cases, integrated multi-disciplinary care would start with the integrated outpatient setting (e.g., the pelvic care centre, the multi-disciplinary pain team) for comorbid (functional) somatic and psychiatric conditions, as evidenced by the findings reported in this thesis<sup>chapter7,38,43,162,163</sup>. The most important part to focus on with regard to complex psychosomatic patients concerning LOS, unplanned hospital readmissions and frequent outpatient care utilization is the transition of inpatient or outpatient hospital care back to primary care<sup>chapter7</sup>. For instance, in complex patients with a pleiotropic presentation of functional somatic complaints, the successful transition of care after intensive outpatient-based psychotherapy may profit from integrated staff-guided CM back to the patients' GPs<sup>35,38,chapter7</sup>. Moving case managers into the frontline of care transition may improve the engagement, compliance and treatment adherence of patients, whose performance may eventually translate into better outcomes and more favourable economic evaluations<sup>2,100,102,chapter7</sup>.

## The Med-Psych-Net - innovativeness, feasibility, implementation and future perspectives

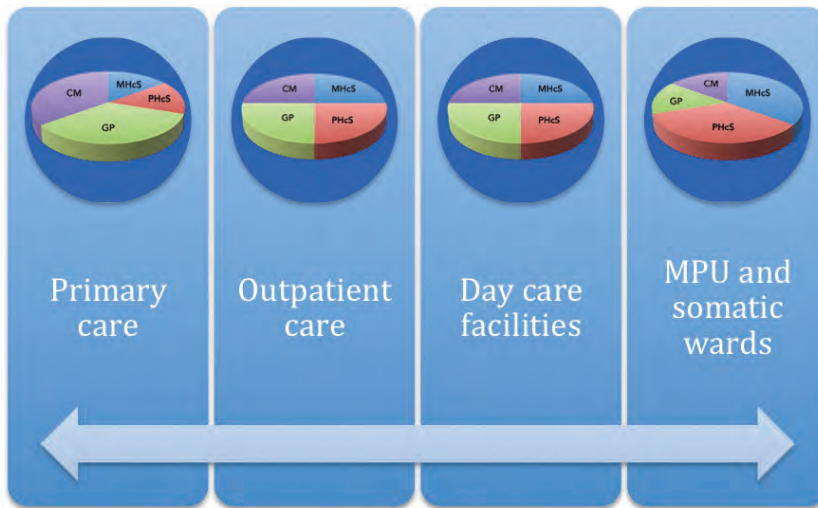
To avoid unintended negative outcomes due to under-detection of psychosomatic complexity or treatment refractoriness in mono-disciplinary care trajectories, integration of care (i.e., bringing together diverse specialty skills and expertise concerning health care in cases of multi-morbidity with comorbid psychiatric and somatic disorders) is deemed necessary at the hospital level and between hospital and primary care. Different organizational aspects of integrated care should be taken into account. The presence of multi-disciplinary teams is indispensable. Furthermore, shared multi-disciplinary clinical protocols and a specialty-transcending information system (with electronically accessible patient files) have to be available. Colocated work would be the ideal arrangement for co-operating services; if not feasible, liaison services operating bi-directionally would be needed to approach the multi-conditional patient. In order to guarantee clinical expertise on a consultant level, navigators (medical staff) and 'steersmen' (care managers) should deliver guidance on the clinical course, either in face-to-face contact with patients and/or care givers or via digital information transferred to patients and their care managers. Furthermore, a multi-component strategy should include efforts to combat stigmatization concerning psychiatric comorbidity<sup>21</sup>.

Various clinical scenarios may illustrate how access to health care can influence patients' outcome negatively. Both low and high levels of access can lead to unplanned readmissions. Patients who are vulnerable from a psychosocial point of view and also show complex multi-morbidity may easily relapse, even if they had received high-quality inpatient care<sup>389</sup>. When these patients receive outpatient care after discharge, they might be less likely to seek timely appointments and more likely to enter the emergency room (ER)<sup>389-391</sup>. With a low level of access to resources that enable self-care and outpatient follow-up, these patients are at a higher risk of readmission and stay in the hospital. Paradoxically, hospitals with expanded access to post-discharge health services also see a rise in unintended readmissions, since increased health care utilization may also occur in multi-conditional patients who lack the resources that enable self-care and are therefore at higher risk of relapse<sup>389,390</sup>. Thus, taking care of the patient and not just the disease is imperative in order to reduce costly hospital stays and unplanned readmissions<sup>20,392</sup>. Primary care-based CM through collaborative care leaves problems with physical well-being unsolved and it is not advisable to treat complex functional conditions in primary care. The solution seems to lie in a hospital-based integrated care model, which incorporates medical staff-guided case management, leading vulnerable complex patients back to primary care<sup>20,35,103,104</sup>. Therefore, we decided to create a psychosomatic network approach, which might be able to increase the patient flow through the hospital and could help bridge the gap between hospital and primary care in order to reduce length of stay or the rate of admissions<sup>43,162,chapter 7,393</sup>.

The Med-Psych-Net consists of the inpatients' MPU, a proactive CLS, different outpatient-based liaison activities (e.g., the multi-disciplinary pain team, the pelvic care

centre) and most importantly the staff-guided CM-based transition of care to GPs. The engineering of care applications that would improve the affordability of hospital care has to incorporate mechanisms that enhance in- and outpatient flow through the medical hospital without proportionately adding staff<sup>393</sup>. Our Med-Psych-Net approach succeeded in that sense. Cost savings have been booked without changing the hospital's fulltime-equivalents among the psychiatry or medical psychology staff, since community mental health service care managers started to join hospital and primary care during that period. With regard to the Med-Psych-Net, it should be kept in mind that these CMHS care givers were only colocated in the MUMC and at GPs and were not additionally employed. For clarification, we engineered a care application that improved the affordability of hospital care via a guided CM mechanism, which enhanced the flow of outpatients through the medical hospital without proportionately adding staff. The Med-Psych-Net is the first comprehensive transitional health care network to address psychosomatic multi-morbidity across various health care settings, starting by picking up patients face-to-face at the medical hospital, as community mental health services' case managers ease the transition from hospital outpatient settings to primary care. In other words, the journey of complex and vulnerable multi-conditional patients across the health care (dis-) continuum has been finalized by placing the role of the hospital within the community context<sup>394,395</sup>. Most programmes targeting care transition assume that hospital readmissions can be reduced by patient empowerment and improved relationships between the hospital and post-acute care settings<sup>394</sup>. The MPN adds another dimension which should not be underestimated: a clinical network approach based on etiologic medical concepts and implemented by medical staff-guidance. The approach might help establish integrated care by connecting specialty outpatient clinics in the hospital. It may also bridge the gap between the hospital and primary care via medical staff-guided transitional care managers without compromising the quality of consultants' etiologic conceptualization or treatment. Thus, in order to guarantee medical expertise across different settings, the MPN facilitates psychosomatic specialty skills in primary care and, vice versa, assures that the general practitioners have an overview of their patients' experiences in the medical hospital. This does not only happen via CMs as a link but also by multi-disciplinary direct or telephone/internet-based medical staff consultations independent from the setting.

Figure 16.3 The Med-Psych-Net - a transitional network approach fostering personalized care in psychosomatic medicine.



Legend: A Med-Psych-Net (MPN) is a virtual network of co-operating care givers who are treating patients with complex psychosomatic conditions, referring them from primary care to the hospital and vice versa. Care givers involved in this integrated approach provide treatment in different proportions depending on the severity and complexity of disease. Patients with the most severe conditions are admitted to the integrated hospital inpatient unit (Med-Psych-Unit (MPU)) or to somatic wards in co-operation with the mental health care consultation-liaison service (CLS). Patients with less impairment but whose medical and/or bio-psychosocial problems are still severe are followed on a day care or outpatient basis. The hospital-related integrated care, ranging from outpatient to inpatient interventions, is covered by the hospital-based Med-Psych-Centre (MPC). Transition of the patient back to primary care takes place at suitable moments when the roles of case manager (CM) and general practitioner (GP) can become more prominent. PHcS = Physical Health care Specialist; MHCs = Mental Health care Specialist.

In order to assess the feasibility of the MPN approach, it is necessary to chart the bottlenecks in psychosomatic complexity care related to primary as well as medical hospital care. As mentioned above, several bottlenecks in primary care are well known: i) the limited consultation time of general practitioners; ii) lack of GPs' specialty skills; iii) the need for a degree of diagnostic openness in psychosomatic patients; and iv) patients' stigma-related resistance to psychosomatic attributions<sup>35</sup>. But others are less well known and are discussed in this thesis. As clinical experience reveals, comorbid mental and somatic illnesses may lead to misdiagnosis, delayed treatment and serious adverse events in the general hospital setting. Several factors have led to misattribution in this regard: i) patients' complex presentation; ii) consultants' lack of concepts concerning complexity; iii) patients' challenging behaviour; iv) clinical pressure due to a crowded medical ward environment; v) patients' resistance to psychosomatic explanations; and

last but not least, vi) the stigmatizing attitude of some staff members<sup>20,351</sup>. In that context, some recommendations may be made to optimize the diagnosis and treatment of multi-conditional patients in the general hospital. In the first place, a pro-active psychiatric CL team has to be available 24 hours a day. This recommendation concurs with in-hospital findings that a pro-active CLS involvement may prevent comorbid patients from going unrecognized<sup>352</sup>. Regarding the subsequent transition back to primary care at the end of hospital stays, GPs' compliance with CLS' recommendations may be enhanced by direct communication between the hospital and primary care providers<sup>353</sup>. Secondly, detailed multi-disciplinary guidelines for the assessment and treatment of multi-conditional patients should be prepared. Thirdly, the hallmark of integrated multi-disciplinary management is to hold regular meetings with staff members from all departments and across all of the settings involved. This should be realized at the in- and outpatient hospital level as well as in primary care to improve clinical reasoning<sup>20,43,354</sup>. Fourthly, the importance of the therapeutic relationship should be emphasized by moving case managers into the frontline of treatment rather than offering mental health or somatic consultation by consultants or GPs alone<sup>2,100,102,355,chapter7</sup>. Last but not least, given the patients' resistance to accepting psychosomatic explanations across all care levels, multi-disciplinary staff-guidance of CMs might help to overcome stigmatization regarding psychosomatic conditions and may guarantee the level of medical expertise across different settings.

Future health care delivery and payment reforms may affect the care of complex multi-conditional patients more than programmes addressing clinical problems in mono-disciplinary settings. Bundled payment for services providing care across settings (i.e., hospital stay and readmission reduction programmes targeting care transition to primary care) should align incentives for hospitals and primary care<sup>394,395</sup>. Given the exploding health care budget and the waiting lists for various hospital interventions in the Netherlands, the Med-Psych-Net approach may achieve multiple goals of care delivery; therefore, it deserves integrated reimbursement. The increasing patient flow through hospitals achieved by the transition of care may reduce frequent care utilization, the length of hospital stay and the amount of unplanned readmissions. Besides achieving favourable patient-related outcomes, the transitional MPN approach could reduce the cost of health care, which might have a societal impact without violating care givers' interests. For instance, the objection voiced by hospitals regarding a loss of income is unfounded. A decrease in the length of hospital stay and in readmissions is accompanied by an increase in first patient consultations at the medical hospital, as evidenced by existing waiting lists. Since health care policy and delivery is increasingly influenced by reimbursement changes to attenuate the health care-related financial burden, new models of care should be evaluated scientifically, taking special note of quality and safety, to minimize unintended outcomes. Thus, future research on care delivery concerning complex or multi-conditional (functional) disorders should take a perspective of complexity science as its point of departure<sup>380</sup>. Disease severity and complexity is



strongly associated with the intensity and frequency of care activities during patients' index admission but also with unintended readmissions<sup>380,386</sup>. The lack of improvement in readmission rates over the past few years indicates that the relationships between risk factors, interventions and intended outcomes are more complex than hitherto acknowledged<sup>380,382</sup>. In addition to current research efforts conducted with an eye to reducing hospital admissions or length of stay, a better scientific approach would entail studying intended outcomes of complex (functional) patients through the lens of complexity science<sup>380</sup>. Its focus is on the identification of participating 'agents', the unpredictability of agent actions, the interactions between multiple agents, and their effect on intended outcomes. In a complex system, it is deemed necessary to look beyond single causative factors and an expected linear response to interventions<sup>380</sup>. By this reasoning, the unintended outcome of unplanned readmissions or a long hospital stay is a result of a series of complex interactions among multiple agents. Hence the need to identify the factors in play: i) the complexity and severity of the underlying disease; ii) patients' openness to a psychosomatic diagnosis; iii) quality of care delivery (at all health care levels) including staffing; iv) co-ordination and continuity of care across settings; v) communication with care participants (between patients and care givers and mutually between care givers); and vi) assessment of the environment into which the patient is discharged<sup>380</sup>. The ability to initiate and sustain an integrated transitional care programme in psychosomatic medicine is increasingly important since the patients' psychosocial factors contribute significantly to the risk of unplanned readmission<sup>396</sup>. The transitional Med-Psych-Net may fulfil its expectations concerning its bridging function. However, the intended outcomes have to be further evaluated with complexity science models. Moreover, a tailored and therefore personalized care model should be constructed by incorporating modern m-health tools into transitional integrated care. Doing so may enable patients and care givers to investigate environmental influences on symptom formation and ways to prevent or overcome stressful threatening events. In this regard, the experience sampling methodology proves to be a valid tool for momentary assessment in complex psychosomatic syndromes<sup>chapter15</sup>. Accordingly, ESM could be applied transdiagnostically for clinical purposes to gain insights that can be used therapeutically, such as in psychotherapeutic trajectories concerning exposure and response prevention in situations of exaggerated harm avoidance. In addition, repeated measures over time using ESM could help to unravel complexity pathways by applying network analysis methodology. In psychiatry, network analysis is currently used to move away from a concept of symptom-based diagnostics in the direction of elementary syndromes. Apparently, 'bridge symptoms' seem to be responsible both for combining symptoms into syndromes and for combining various syndromes into a network structure<sup>397</sup>. In that sense, complexity science may not only improve the efficacy of network approaches with regard to care delivery but might also explain comorbidity patterns. Therefore, network models may predict the clinical course of multi-morbidity phenotypes and might thus help to designate state- and

severity-related targets for complexity interventions. As in psychosis, affective symptoms may act as central network symptoms<sup>398</sup>, thereby moderating or amplifying complex (functional) somatic complaints and care utilization accordingly since stress-related disorders are associated with an increase in direct and indirect costs, depending on the complexity (i.e., comorbidity) and the severity of symptoms<sup>399,400</sup>. Regarding potential causation, cumulative serious life threat has been linked with both mental and physical complaints and is associated with an increased number of doctor visits and hospital admissions<sup>401</sup>. However, the individual variation in the temporal relationship between stress and complex functional somatic conditions and the dynamics of the body's stress matrix warrant further investigation to elucidate the temporal complexity between stress and multi-conditional complaints over time<sup>402,403</sup>. Subjecting temporal complexity to time series analysis might contribute to the discovery of complexity pathways and, more importantly, to patient-tailored treatment<sup>402</sup>. A complex functional somatic syndrome shows very high frequencies of comorbid mental disorders at the specialized hospital outpatient level (i.e., affective conditions and somatoform disorders presenting with almost equal prevalence). In that light, the presence of multiple physical symptoms is longitudinally associated with the recurrence of affective conditions at the community, primary care or mental health care level. The question then arises: What comes first – the chicken or the egg (i.e., complex (functional) somatic or affective complaints)<sup>42,404-406</sup>? Following patients through various health care settings (e.g., via the Med-Psych-Net) by using the same patient-related mobile/e-health assessment tool across medical settings (e.g., ESM) might elucidate the sequence of complexity development and help answer the next question: What is (dys-) functional in complex functional somatic syndromes? From a systemic point of view, complex functional somatic conditions with comorbid affective disorders are probably best understood as a sensitized defence response to earlier threats resulting in perceived emotional and bodily distress (i.e., hyperarousal). Besides psychological stressors, physical threat contributes to an alarm falsification in the body–brain crosstalk, affecting mood, cognition and defensive behaviour -- the symptoms of affective and functional somatic disorders<sup>38</sup>. In order to further investigate the relation between contextual threat and symptom formation, a feasible and reliable momentary assessment tool for diagnostic and therapeutic purposes (i.e., ESM) can be implemented. ESM has been shown to be a reliable transdiagnostic mROM tool, which also can be used to facilitate shared decision making and monitoring of personalized treatment in psychosomatic medicine<sup>chapter15</sup>.

With regard to integrated complexity treatment, MPUs embedded in a transitional Med-Psych-Net might help to reassess the consistent evidence for the negative association between concomitant physical symptoms and affective conditions in order to turn the course of affective conditions at the highest level of complexity. Moreover, the Med-Psych-Net may add value in the light of the fragile consensus between patients with comorbid conditions and health care professionals on the preventability of costly readmissions<sup>20,37,407-409</sup>. At moments of care transition, staff-guided case management

supported by ESM can take over the care, eventually leading to primary care-based collaborative care<sup>chapter7&15</sup>. In the temporal relationship between stress and complex functional somatic conditions, the most care-relevant moment might be when complexity gets started. At that moment of initial complexity, the exclusive administration of web-based telemedicine or m-health management is a scenario that deserves further investigation, even with regard to multi-conditional complaints. The rationale is that patients with an initial but increasing somatic symptom burden rise instantly to the same level of health care utilization as patients with chronic physical symptoms<sup>410-412</sup>. Alternatively, immediate involvement of an integrated Med-Psych-Net approach should be considered if patients and primary care givers need medical staff-guided CM to establish psychosomatic attributions.

## References

1. Sharpe, M & Naylor, C. Integration of mental and physical health care: From aspiration to practice. *Lancet Psychiatry* 3, 312-313 (2016).
2. Kroenke, K. & Unützer, J. Closing the false divide: Sustainable approaches to integrating mental health services into primary care. *J. Gen. Intern. Med.* 32, 404-410 (2016).
3. Kathol, R. G. Cost outcomes on a medical psychiatry unit. *J. Psychosom. Res.* 68, 293-294 (2010).
4. Hall, R. & Kathol, R. Developing a level III/IV medical psychiatric unit: Establishing a basis, design of the unit and physician responsibility. *Psychosomatics* 33, 368-375 (1992).
5. Campo, J. V. & Raney, D. The pediatric medical-psychiatric unit in a psychiatric hospital. *Psychosomatics* 36, 438-444 (1995).
6. Nomura, S. *et al.* Evaluation of the first medical psychiatric unit in Japan. *Psychiatry Clin. Neurosci.* 50, 305-308 (1996).
7. Fennig, S. & Fennig, S. Management of encopresis in early adolescence in a medical psychiatric unit. *Gen. Hosp. Psychiatry* 21, 360-367 (1999).
8. Kishi, Y. & Kathol, R. Integrating medical and psychiatric treatment in an inpatient medical setting: The type IV program. *Psychosomatics* 40, 345-355 (1999).
9. van Waarde, J. *et al.* The medical psychiatric unit: Added value for patients, physicians and hospitals. *Ned. Tijdschr. Geneesk.* 148, 209-211 (2004).
10. Hanna, S. J. *et al.* The coming of age of a joint elderly medicine-psychiatric ward: 18 years experience. *Int. J. Clin. Pract.* 62, 146-151 (2008).
11. Honig, A. *et al.* A medical-psychiatric unit in a general hospital: Effective combined somatic and psychiatric care? *Ned Tijdschr. Geneesk.* 158, A6520 (2014).
12. Young, L. & Harsch, H. H. Length of stay on a psychiatry medicine unit. *Gen. Hosp. Psychiatry* 11, 31-35 (1989).
13. Goldberg, R. & Simundson, S. Managing Medicare reimbursement on medical psychiatry units. *Gen. Hosp. Psychiatry* 13, 313-318 (1991).
14. Üstün, T. B. *et al.* Global burden of depressive disorder in the year 2000. *Br. J. Psychiatry* 184, 386-392 (2004).
15. Meyer, T. *et al.* Depression but not anxiety is a significant predictor of physicians' assessments of medical status in physically ill patients. *Psychother. Psychosom.* 69, 147-154 (2000).
16. Kroenke, K. *et al.* Depressive and anxiety disorders in patients with physical complaints: Clinical predictors and outcome. *Am. J. Med.* 103, 339-347 (1997).
17. Sharpe, M. *et al.* Is co-morbid depression adequately treated in patients repeatedly referred to specialist medical services with symptoms of a medical condition? *J. Psychosom. Res.* 72, 419-421 (2012).
18. Robinson, R. L. *et al.* Covariates of depression and high utilizers of healthcare: Impact on resource use and costs. *J. Psychosom. Res.* 85, 35-43 (2016).
19. Schieveld, J. N. *et al.* Pediatric illness severity measures predict delirium in a pediatric intensive care unit. *Crit. Care Med.* 36, 1933-1936 (2008).
20. Leue C, *et al.* Managing complex patients on a Medical Psychiatric Unit: An observational study of university hospital costs associated with medical service use, length of stay and psychiatric intervention. *J. Psychosom. Res.* 68, 295-302 (2010).
21. Rodgers, M. *et al.* Integrated care to address the physical health needs of people with severe mental illness - a rapid review. Southampton (UK): NIHR Journals Library (2016).
22. Hussain, M. & Seitz, D. Integrated models of care for medical inpatients with psychiatric disorders: A systematic review. *Psychosomatics* 55, 315-325 (2014).
23. Gemmill, E. H. & McCulloch, P. Systematic review of minimally invasive resection for gastro-oesophageal cancer. *Br. J. Surg.* 94, 1461-1467 (2007).
24. Kane, R. L. *et al.* The association of registered nurse staffing levels and patient outcomes: Systematic review and meta-analysis. *Med. Care.* 45, 1195-1204 (2007).
25. Kinder, L. S. *et al.* Improving depression care in patients with diabetes and multiple complications. *J. Gen. Intern. Med.* 21, 1036-1041 (2006).

26. Katon, W. J. *et al.* The Pathway Study: A randomized trial of collaborative care in patients with diabetes and depression. *Arch. Gen. Psychiatry* 61, 1042-1049 (2004).
27. Wilson, T. & Holt, T. Complexity and clinical care. *BMJ*. 323, 685-688 (2001).
28. Stewart, M. Continuity, care and commitment: The course of patient-clinician relationships. *Ann. Fam. Med.* 2, 388-390 (2004).
29. de Jonge, P. *et al.* Care complexity in the general hospital: Results from a European study. *Psychosomatics* 42, 204-212 (2001).
30. Kathol, R. *et al.* Epidemiologic trends and costs of fragmentation. *Med. Clin. N. Am.* 90, 549-572 (2006).
31. Huysse, F. J. *et al.* Identifiers, or "red flags," of complexity and need for integrated care. *Med. Clin. North Am.* 90, 703-712 (2006).
32. Lobo, E. *et al.* Identification of components of health complexity on internal medicine units by means of the INTERMED method. *Int. J. Clin. Pract.* 69, 1377-1386 (2015).
33. Huffman, J. C. *et al.* Essential articles on collaborative care models for the treatment of psychiatric disorders in medical settings: A publication by the academy of psychosomatic medicine research and evidence-based practice committee. *Psychosomatics* 55, 109-122 (2014).
34. Hiller, W. *et al.* A controlled treatment study of somatoform disorders including analysis of healthcare utilization and cost-effectiveness. *J. Psychosom. Res.* 54, 369-380.
35. Rosendal, M. *et al.* Enhanced care by generalists for functional somatic symptoms and disorders in primary care. *Cochrane Database Syst. Rev.* 10, CD008142 (2013).
36. Janse, B. *et al.* Delivering integrated care for the frail elderly: The impact on professionals' objective burden and job satisfaction. *Int.J. Integr. Care* 16:7 (2016).
37. van Schijndel, M. A. *et al.* Medical-psychiatric units in the Netherlands: An investigation into distribution and quality. *Ned. Tijdschr. Geneesk.* 161, D890 (2017).
38. Leue, C. *et al.* Functional urological disorders: A sensitized defence response in the bladder-gut-brain axis. *Nat.Rev. Urol.* 14, 153-163 (2017).
39. Sood, R. & Ford, A. C. Rome IV criteria for FGIDs – an improvement or more of the same? *Nat. Rev. Gastroenterol.Hepatol.*13, 501-502 (2016).
40. Van Dessel, N. *et al.* The PROSPECTS study: Design of a prospective cohort study on prognosis and perpetuating factors of medically unexplained physical symptoms (MUPS). *J. Psychosom. Res.* 76, 200-206 (2014).
41. Verdonshot, R. J. *et al.* Symptoms of anxiety and depression assessed with the Hospital Anxiety and Depression Scale in patients with oropharyngeal dysphagia. *J. Psychosom. Res.* 75, 451-455 (2013).
42. Brünahl, C. *et al.* Mental disorders in patients with chronic pelvic pain syndrome (CPPS). *J. Psychosom. Res.* 98, 19-26 (2017).
43. Kruijmel, J. *et al.* Integrated medical-psychiatric outpatient care in functional gastrointestinal disorders improves outcome: A pilot study. *Eur. J. Gastroenterol. Hepatol.* 27, 721-727 (2015).
44. Fink, P. *et al.* Somatization in primary care. Prevalence, health care utilization, and general practitioner recognition. *Psychosomatics* 40, 330-338 (1999).
45. Hahn, S. R. *et al.* The difficult doctor-patient relationship: Somatization, personality and psychopathology. *J. Clin. Epidemiol.* 47, 647-657 (1994).
46. Smith, B. J. *et al.* The identification in primary care of patients who have been repeatedly referred to hospital for medically unexplained symptoms: a pilot study. *J. Psychosom. Res.* 67, 207-211 (2009).
47. Smith, R. C. & Dwamena, F. C. Classification and diagnosis of patients with medically unexplained symptoms. *J. Gen. Intern. Med.* 22, 685-691 (2007).
48. Ferrari, S. *et al.* Vertigo "in the pink": The impact of female gender on psychiatric-psychosomatic comorbidity in benign paroxysmal positional vertigo patients. *Psychosomatics* 55, 280-288 (2014).
49. <http://www.cbo.nl>
50. <http://kims.orde.nl/het-kennisinstituut-voor-u/richtlijnen/>
51. Murray, A. M. *et al.* Barriers to the diagnosis of somatoform disorders in primary care: Protocol for a systematic review of the current status. *Syst. Rev.* 2, 99 (2013).
52. Murray, A. M. *et al.* The challenge of diagnosing non-specific, functional, and somatoform disorders: A systematic review of barriers to diagnosis in primary care. *J. Psychosom. Res.* 80, 1-10 (2016).

53. Milsom, I. *et al.* Epidemiology of urinary incontinence (IU) and other lower urinary tract symptoms (LUTS), pelvic organ prolapse (POP) and anal incontinence. In: Abrams P, editor. *Incontinence* 5th ed, 15-108 (2013).
54. Luber, K. M. *et al.* The demographics of pelvic floor disorders: Current observations and future projections. *Am. J. Obstet. Gynecol.* 184, 1496-1501 (2001).
55. Davis, K. J. *et al.* Pelvic floor dysfunction: A scoping study exploring current service provision in the UK, interprofessional collaboration and future management priorities. *Int. J. Clin. Pract.* 64, 1661-70 (2010).
56. Berghmans, B. *et al.* Prevalence and triage of first-contact complaints on pelvic floor dysfunctions in female patients at a Pelvic Care Centre. *NeuroUrol. Urodyn.* 35, 503-508 (2015).
57. Coyne, K. S. *et al.* National community prevalence of overactive bladder in the United States stratified by sex and age. *Urology* 77, 1081-1087 (2011).
58. Abrams, P. *et al.* The standardisation of terminology in lower urinary tract function: Report from the standardisation sub-committee of the International Continence Society. *Urology* 61, 37-49 (2003).
59. Vrijens, D. *et al.* Affective symptoms and the overactive bladder: A systematic review. *J. Psychosom. Res.* 78, 95-108 (2015).
60. Melville, J. L. *et al.* Incontinence severity and major depression in incontinent women. *Obstet. Gynecol.* 106, 585-592 (2005).
61. Leue, C. *et al.* Bidirectional associations between depression/anxiety and bowel disease in a population based cohort. *J. Epidemiol. Community Health* 59, 434 (2005).
62. Fukudo, S. *et al.* Evidence-based clinical practice guidelines for irritable bowel syndrome. *J. Gastroenterol.* 50, 11-30 (2015).
63. Fink, P. *et al.* The prevalence of somatoform disorders among internal medical inpatients. *J. Psychosom. Res.* 56, 413-418 (2004).
64. Chatoor, D. *et al.* Organising a clinical service for patients with pelvic floor disorders. *Best Pract. Res. Clin. Gastroenterol.* 23, 611-620 (2009).
65. Zigmond, A. S. & Snaith, R. P. The hospital anxiety and depression scale. *Acta Psychiatr Scand.* 67, 361-370 (1983).
66. Clemens, J. Q. *et al.* The MAPP research network: A novel study of urologic chronic pelvic pain syndromes. *Bmc Urol.* 14, doi: 10.1186/1471-2490-14-57 (2014).
67. Cardoso, G. *et al.* Depression and anxiety symptoms following cancer diagnosis: A cross-sectional study. *Psychol. Health Med.* 21, 562-570 (2016).
68. Coyne, K. S. *et al.* The impact of overactive bladder on mental health, work productivity and health-related quality of life in the UK and Sweden: Results from EpiLUTS. *BJU Int.* 108, 1459-1471 (2011).
69. Perry, S. *et al.* An investigation of the relationship between anxiety and depression and urge incontinence in women: Development of a psychological model. *Br. J. Health Psychol.* 11, 463-482 (2006).
70. Ghetti, C. *et al.* Depressive symptoms in women seeking surgery for pelvic organ prolapse. *Int. Urogynecol. J.* 21, 855-860 (2010).
71. Ghetti, C. *et al.* The emotional burden of Pelvic Organ Prolapse in women seeking treatment: a qualitative study. *Female Pelvic Med. Reconstr. Surg.* 21, 332-338 (2015).
72. Di Gangi Herms, A. M. *et al.* Assessing health care needs and clinical outcome with urological case complexity: A study using INTERMED. *Psychosomatics* 44, 196-203 (2003).
73. Balachandran, A. *et al.* Management of female urinary incontinence: a survey of urogynaecologists' view on the NICE guideline. *J. Obstet. Gynaecol.* 36, 487-491 (2016).
74. Walker, J. *et al.* Screening medical patients for depression: Lessons from a national program in cancer clinics. *Psychosomatics* pii: S0033-3182(17)30007-5 (2017).
75. Bjelland, I. *et al.* The validity of the Hospital Anxiety and Depression Scale: An updated literature review. *J. Psychosom. Res.* 52, 69-77 (2002).
76. Penninx, B. W. *et al.* Depression and cardiac mortality: Results from a community-based longitudinal study. *Arch. Gen. Psychiatry* 58, 221-227 (2001).
77. Roy-Byrne, P. P. *et al.* Anxiety disorders and comorbid medical illness. *Gen. Hosp. Psychiatry* 30, 208-225 (2008).
78. Maserejian, N. N. *et al.* Treatment status and risk factors for incidence and persistence of urinary incontinence in women. *Int. Urogynecol. J.* 25, 775-782 (2014).

79. Bogner, H. R. *et al.* Anxiety disorders and disability secondary to urinary incontinence among adults over age 50. *Int. J. Psychiatry Med.* 32, 141-154 (2002).
80. Talley, N. J. Functional gastrointestinal disorders as a public health problem. *Neurogastroenterol. Motil.* 20 (Suppl 1), 121-129 (2008).
81. Fortea, J. & Prior, M. Irritable bowel syndrome with constipation: A European-focused systematic literature review of disease burden. *J. Med. Econ.* 16, 329-41 (2013).
82. Agarwal, N. & Spiegel, B. M. The effect of irritable bowel syndrome on health-related quality of life and health care expenditures. *Gastroenterol. Clin. North Am.* 40, 11-19 (2011).
83. Stanghellini, V. *et al.* Dyspeptic symptoms and gastric emptying in the irritable bowel syndrome. *Am. J. Gastroenterol.* 97, 2738-2743 (2002).
84. Van der Veek, P. P. *et al.* Symptom severity but not psychopathology predicts visceral hypersensitivity in irritable bowel syndrome. *Clin. Gastroenterol. Hepatol.* 6, 321-328 (2008).
85. Camilleri, M. & Gorman, H. Intestinal permeability and irritable bowel syndrome. *Neurogastroenterol. Motil.* 19, 545-552 (2007).
86. Villani, A. C. *et al.* Genetic risk factors for post-infectious irritable bowel syndrome following a waterborne outbreak of gastroenteritis. *Gastroenterology* 138, 1502-1513 (2010).
87. Drossman, D. A. *et al.* Psychosocial aspects of the functional gastrointestinal disorders. *Gut* 45, 1125-30 (1999).
88. Mykletun, A. *et al.* Prevalence of mood and anxiety disorder in self-reported irritable bowel syndrome (IBS): An epidemiological population based study of women. *BMC Gastroenterology* 10, 88 (2010).
89. Neeleman, J. *et al.* The distribution of psychiatric and somatic ill health: Associations with personality and socioeconomic status. *Psychosom. Med.* 63, 239-247 (2001).
90. Levy, R. L. *et al.* Psychosocial aspects of the functional gastrointestinal disorders. *Gastroenterology* 130, 1447-1458 (2006).
91. Stidd, D. A. *et al.* Spinal cord stimulation with implanted epidural paddle lead relieves chronic axial low back pain. *J. Pain. Res.* 7, 465-470 (2014).
92. Lihua, P. *et al.* Spinal cord stimulation for cancer related pain in adults. *Cochrane Database Syst. Rev.* 2, CD009389 (2013).
93. Noblett, K. *et al.* Results of a prospective multicenter Study evaluating quality of life, safety, and efficacy of sacral neuromodulation at twelve months in subjects with symptoms of overactive bladder. *Neurourol. Urodyn.* 35, 246-251 (2016).
94. Ford, A. C. *et al.* Efficacy of antidepressants and psychological therapies in irritable bowel syndrome: Systematic review and meta-analysis. *Gut* 58, 367-378 (2009).
95. Ford, A. C. *et al.* Effect of antidepressants and psychological therapies, including hypnotherapy, in irritable bowel syndrome: Systematic review and meta-analysis. *Am. J. Gastroenterol.* 109, 1350-1365 (2014).
96. ClinicalTrials.gov Protocol Registration System; Identifier:NCT01551225.
97. Chapman, S. J. *et al.* Discontinuation and non-publication of surgical randomised controlled trials: An observational study. *BMJ* 349, g6870 (2014).
98. Ebrahim, S. *et al.* Reanalyses of randomized clinical trial data. *JAMA* 312, 1024-1032 (2014).
99. Schweckhardt, A. *et al.* Short-term psychotherapeutic interventions for somatizing patients in the general hospital: A randomized controlled study. *Psychother. Psychosom.* 76, 339-346 (2007).
100. Katon, W. J. *et al.* Collaborative care for patients with depression and chronic illnesses. *N. Engl. J. Med.* 363, 2611-2620 (2010).
101. Katon, W. *et al.* Cost-effectiveness of a multicondition collaborative care intervention: A randomized controlled trial. *Arch. Gen. Psychiatry* 69, 506-514 (2012).
102. Reed, S. J. *et al.* Effectiveness and value of integrating behavioral health into primary care. *JAMA Intern. Med.* 176, 691-692 (2016).
103. Archer, J. *et al.* Collaborative care for depression and anxiety problems. *Cochrane Database Syst. Rev.* 10:CD006525 (2012).
104. Tully, P. J. & Baumeister, H. Collaborative care for comorbid depression and coronary heart disease: A systematic review and meta-analysis of randomised controlled trials. *BMJ Open* 5, e009128 (2015).
105. Smith, S. M. *et al.* Interventions for improving outcomes in patients with multimorbidity in primary care and community settings. *Cochrane Database Syst. Rev.* 3, CD006560 (2016).

106. Lofors, J. & Sundquist, K. Low-linking social capital as a predictor of mental disorders: A cohort study of 4.5 million Swedes. *Soc. Sci. Med.* 64, 21-34 (2007).
107. Thomas, H. *et al.* Mental health and quality of residential environment. *Br. J. Psychiatry* 191, 500-505 (2007).
108. Ivory, V. C. *et al.* When does neighbourhood matter? Multilevel relationships between neighbourhood social fragmentation and mental health. *Soc. Sci. Med.* 72, 1993-2002 (2011).
109. Lederbogen, F. *et al.* City living and urban upbringing affect neural stress processing in humans. *Nature* 474, 498-501 (2011).
110. Hubbard, C. *et al.* Corticotropin-releasing factor receptor 1 antagonist alters regional activation and effective connectivity in an emotional-arousal circuit during expectation of abdominal pain. *J. Neurosci.* 31, 12491-12500 (2011).
111. Murrrough, J. W. *et al.* Reduced amygdala serotonin transporter binding in posttraumatic stress disorder. *Biol. Psychiatry* 70, 1033-1038 (2011).
112. Smith, H. S. *et al.* Fibromyalgia: an afferent processing disorder leading to a complex pain generalized syndrome. *Pain Physician* 14, E217-245 (2011).
113. Price, D. D, *et al.* Widespread hyperalgesia in irritable bowel syndrome is dynamically maintained by tonic visceral impulse input and placebo/nocebo factors: Evidence from human psychophysics, animal models and neuroimaging. *Neuroimage* 47, 995-1001 (2009).
114. Wise, T. N. *et al.* Painful physical symptoms in depression: A clinical challenge. *Pain Med.* 8 (Suppl 2), 75-82 (2007).
115. Goldenberg DL. Pain/Depression dyad: A key to a better understanding and treatment of functional somatic syndromes. *Am. J. Med.* 123, 675-682 (2010).
116. Peen, J. *et al.* The current status of urban-rural differences in psychiatric disorders. *Acta Psychiatr. Scand.* 121, 84-93 (2010).
117. Crump, C. *et al.* Neighborhood deprivation and psychiatric medication prescription: A Swedish national multilevel study. *Ann. Epidemiol.* 21, 231-237.
118. Drukker, M. & van Os, J. Mediators of neighbourhood socioeconomic deprivation and quality of life. *Soc. Psychiatry Psychiatr. Epidemiol.* 38, 698-706 (2003).
119. Skapinakis, P. *et al.* Socio-economic position and common mental disorders: Longitudinal study in the general population in the UK. *Br. J. Psychiatry* 189, 109-117 (2006).
120. March, D. *et al.* Psychosis and place. *Epidemiol. Rev.* 30, 84-100 (2008).
121. Hotopf, M. *et al.* Temporal relationships between physical symptoms and psychiatric disorder: Results from a national birth cohort. *Br. J. Psychiatry* 173, 255-261 (1998).
122. Barsky, A. J. *et al.* Somatization increases medical utilization and costs independent of psychiatric and medical comorbidity. *Arch. Gen. Psychiatry* 62, 903-910 (2005).
123. Freedenfeld, R. N. *et al.* Decreased pain and improved quality of life in fibromyalgia patients treated with olanzapine, an atypical neuroleptic. *Pain Pract.* 6, 112-118 (2006).
124. Seidel, S. *et al.* Antipsychotics for acute and chronic pain in adults. *Cochrane database Syst. Rev.* 4, CD004844 (2008).
125. Kim, K. W. *et al.* Association between comorbid depression and osteoarthritis symptom severity in patients with knee osteoarthritis. *J. Bone Joint. Surg. Am.* 93, 556-563 (2011).
126. Maniadas, N. & Gray, A. The economic burden of back pain in the UK. *Pain* 84, 95-103 (2000).
127. de Jonge, P. *et al.* Case and Care Complexity in the Medically Ill. *Med. Clin. North Am.* 90, 679-692 (2006).
128. Seal, K. H. *et al.* Association of mental health disorders with prescription opioids and high-risk opioid use in US veterans of Iraq and Afghanistan. *JAMA* 307, 940-947 (2012).
129. Bohnert, A. S. *et al.* Association between opioid prescribing patterns and opioid overdose-related deaths. *JAMA* 305, 1315-1321 (2011).
130. Dersh, J. *et al.* Chronic pain and psychopathology: Research findings and theoretical considerations. *Psychosom. Med.* 64, 773-786 (2002).
131. Edit, V. *et al.* Psychosocial, educational, and somatic factors in chronic non-specific low back pain. *Rheumatol. Int.* 33, 587-592(2013).
132. Vargas-Schaffer G. Is the WHO analgesic ladder still valid? Twenty-four years of experience. *Can. Fam. Physician* 56, 514-517 (2010).



133. Häuser, W. *et al.* Treatment of fibromyalgia syndrome with antidepressants: A meta-analysis. *JAMA* 301, 198-209 (2009).
134. Saarto, T. & Wiffen, P. J. Antidepressants for neuropathic pain. *Cochrane database Sys. Rev.* 4, CD005454 (2007).
135. Krebs, E. E. *et al.* Treating the physical symptoms of depression with second-generation antidepressants: A systematic review and meta-analysis. *Psychosomatics* 49, 191-198 (2008).
136. Arnold, L. M. *et al.* Comparisons of the efficacy and safety of duloxetine for the treatment of fibromyalgia in patients with versus without major depressive disorder. *Clin. J. Pain* 25, 461-468 (2009).
137. Arnold, L. M. *et al.* Comorbidity of fibromyalgia and psychiatric disorders. *J Clin. Psychiatry* 67, 1219-1225 (2006).
138. Bekhit MH. Opioid-induced hyperalgesia and tolerance. *Am. J. Ther.* 17, 498-510 (2010).
139. Berton, O. *et al.* Essential role of BDNF in the mesolimbic dopamine pathway in social defeat stress. *Science* 311, 864-868 (2006).
140. Upadhyay, J. *et al.* Alterations in brain structure and functional connectivity in prescription opioid-dependent patients. *Brain* 133, 2098-2114 (2010).
141. Angst, M. S. & Clark, J. D. Opioid-induced hyperalgesia: A qualitative systematic review. *Anesthesiology* 104, 570-587 (2006).
142. Rayner, L. *et al.* Antidepressants for depression in physically ill people. *Cochrane database Sys Rev* 3, CD007503 (2010).
143. van der Feltz-Cornelis, C. M. Ten years of integrated care for mental disorders in the Netherlands. *Int. J. Integr. Care SpecEd:* e015 (2011).
144. Leue, C. *et al.* Observational evidence that urbanisation and neighbourhood deprivation are associated with escalation in chronic pharmacological pain treatment: A longitudinal population-based study in the Netherlands. *BMJ Open* 2: e101136 (2012).
145. Simon, G. E. & Walker E. A. The primary care clinic. The American Psychiatric Publishing Textbook of Consultation-Liaison Psychiatry: Psychiatry in the Medically Ill, 2nd Edition. Edited by Wise, M. G. & Rundell, J. R. Washington, DC, American Psychiatric Publishing, 917-925 (2002).
146. Hall, R. C. *et al.* Cost-effectiveness of the consultation-liaison service. The American Psychiatric Publishing Textbook of Consultation-Liaison Psychiatry: Psychiatry in the Medically Ill, 2nd Edition. Edited by Wise, M. G. & Rundell, J. R. Washington, DC, American Psychiatric Publishing, 25-32 (2002).
147. Saravay, S. M. & Lavin, M. Psychiatric comorbidity and length of stay in the general hospital. A critical review of outcome studies. *Psychosomatics* 35, 233-252 (1994).
148. Druss, B. G. & Rosenheck, R. A. Patterns of health care costs associated with depression and substance abuse in a national sample. *Psychiatr. Serv.* 50, 214-218 (1999).
149. Stiefel, F. *et al.* Effects of a multifaceted psychiatric intervention targeted for complex medically ill: A randomized controlled trial. *Psychother. Psychosom.* 77, 247-256 (2008).
150. Desan, P. H. *et al.* Proactive psychiatric consultation services reduce length of stay for admission to an inpatient medical team. *Psychosomatics* 52,513-520 (2011).
151. Foy, R. *et al.* Meta-analysis: Effect of interactive communication between collaborating primary care physicians and specialists. *Ann. Intern. Med.* 152, 247-258 (2010).
152. Holland, D. E. *et al.* Problems and unmet needs of patients discharged "home to self-care". *Prof. Case Manag.* 16, 240-250 (2011).
153. Mesteig, M. *et al.* Unwanted incidents during transition of geriatric patients from hospital to home: A prospective observational study. *BMC Health Serv. Res.* 10: doi: 10.1186/1472-6963-10-1 (2010).
154. Prvu Bettger, J. *et al.* Transitional care after hospitalization for acute stroke or myocardial infarction: A systematic review. *Ann. Intern. Med.* 157, 407-416 (2012).
155. Horwitz, L. I. *et al.* Quality of discharge practices and patient understanding at an academic medical center. *JAMA Intern. Med.* 173, 1715-1722 (2013).
156. Coleman, E. A. *et al.* The care transitions intervention: Results of a randomized controlled trial. *Arch. Intern. Med.* 166, 1822-1828 (2006).
157. Jackson, C. T. *et al.* Transitional care cut hospital readmissions for North Carolina Medicaid patients with complex chronic conditions. *Health Aff.* 32, 1407-1415 (2013).

158. Schaefer, R. *et al.* Specific collaborative group intervention for patients with medically unexplained symptoms in general practice: A cluster randomized controlled trial. *Psychother. Psychosom.* 82, 106-119 (2013).
159. Kathol, R. G. *et al.* Psychiatrists for medically complex patients: Bringing value at the physical health and mental health/substance-use disorder interface. *Psychosomatics* 50, 93-107 (2009).
160. Leentjens, A. F. *et al.* Can we increase adherence to treatment recommendations of the consultation psychiatrist working in a general hospital? A systematic review. *J. Psychosom. Res.* 68, 303-309 (2010).
161. Van der Feltz-Cornelis, C. M. *et al.* Effect of psychiatric consultation models in primary care. A systematic review and meta-analysis of randomized clinical trials. *J. Psychosom. Res.* 68, 521-533 (2010).
162. Vrijens, D. *et al.* Prevalence of anxiety and depressive symptoms and their association with pelvic floor dysfunctions: A cross sectional cohort study at a Pelvic Care Centre. *NeuroUrol. Urodyn.* doi: 10.1002/nau.23186 (2017).
163. Baijens, L. W. *et al.* Medically unexplained otorhinolaryngological symptoms: Towards integrated psychiatric care. *Laryngoscope* 125, 1583-1587 (2015).
164. DiMatteo, M. R. *et al.* Depression is a risk factor for non-compliance with medical treatment: Meta-analysis of the effects of anxiety and depression on patient adherence. *Arch. Intern. Med.* 160, 2101-07 (2000).
165. Unutzer, J. *et al.* Long-term cost effects of collaborative care for late-life depression. *Am. J. Manag. Care.* 14, 95-100 (2008).
166. Wells, K. B. *et al.* Psychiatric disorder in a sample of the general population with and without chronic medical conditions. *Am. J. Psychiatry* 145, 976-981 (1988).
167. Katon, W. J. Clinical and health services relationships between major depression, depressive symptoms, and general medical illness. *Biol. Psychiatry* 54, 216-226 (2003).
168. Katon, W. J. Epidemiology and treatment of depression in patients with chronic medical illness. *Dialogues Clin. Neurosci.* 13, 7-23 (2011).
169. Neeleman, J. *et al.* Propensity to psychiatric and somatic ill health: Evidence from a birth cohort. *Psychol. Medicine* 32, 793-803 (2002).
170. Härter, M. *et al.* Increased 12-month prevalence rates of mental disorders in patients with chronic somatic diseases. *Psychother. Psychosom.* 76, 354-360 (2007).
171. Konnopka, A. *et al.* Economics of medically unexplained symptoms: A systematic review of the literature. *Psychother. Psychosom.* 81, 265-275 (2012).
172. Cuijpers, P. *et al.* Economic costs of neuroticism: A population-based study. *Arch. Gen. Psychiatry* 67, 1086-1093 (2010).
173. Mitchell, A. J. Systematic review: Depression screening and management programmes with staff assistance in primary care increase response and remission rates, but programmes without staff assistance do not show benefits. *Evid. Based Med.* 15, 49-50 (2010).
174. Magdelijns, F. J. *et al.* Unplanned readmissions in younger and older adult patients: The role of healthcare-related adverse events. *Eur. J. Med. Res.* 21, 35 (2016).
175. Magdelijns, F. J. *et al.* Direct health care costs of hospital admissions due to adverse events in The Netherlands. *Eur. J. Public Health.* 24, 1028-1033 (2014).
176. Henningsen, P. *et al.* Medically unexplained physical symptoms, anxiety and depression: A meta-analytic review. *Psychosom. Med.* 65, 528-533 (2003).
177. Rickards H. Depression in neurological disorders: Parkinson's disease, multiple sclerosis, and stroke. *J. Neurol. Neurosurg. Psychiatry* 76, i48-i52 (2005).
178. Hammerlid, E. & Taft, C. Health-related quality of life in long-term head and neck cancer survivors: A comparison with general population norms. *Br. J. Cancer* 84, 149-56 (2001).
179. Ronis, D. L. *et al.* Changes in quality of life over 1 year in patients with head and neck cancer. *Arch. Otolaryngol. Head Neck Surg.* 134, 241-248 (2008).
180. De Graeff, A. *et al.* Long-term quality of life of patients with head and neck cancer. *Laryngoscope* 110, 98-106 (2000).
181. Rogus-Pulia, N. M. *et al.* Changes in swallowing physiology and patient perception of swallowing function following chemoradiation for head and neck cancer. *Dysphagia* 29, 223-233 (2014).
182. Troche, M. S. *et al.* Decreased cough sensitivity and aspiration in Parkinson's disease. *Chest* 146, 1294-1299 (2014).

183. Mu, L. *et al.* Parkinson disease affects peripheral sensory nerves in the pharynx. *J. Neuropathol. Exp. Neurol.* 72, 614-623 (2013).
184. Onofri, SM. *et al.* Correlation between laryngeal sensitivity and penetration/aspiration after stroke. *Dysphagia* 29, 256-261 (2014).
185. Manikantan K, Khode S, Sayed SI *et al.* Dysphagia in head and neck cancer. Complications of treatment. *Cancer Treat. Rev.* 35, 724-732 (2009).
186. Jäghagen, A. L. *et al.* Pharyngeal swallowing dysfunction following treatment for oral and pharyngeal cancer association with diminished intraoral sensation and discrimination ability. *Head Neck* 10, 1344-1351 (2008).
187. Ku, P. K. *et al.* Laryngopharyngeal sensory deficits and impaired pharyngeal motor function predict aspiration in patients irradiated for nasopharyngeal carcinoma. *Laryngoscope* 120, 223-228 (2009).
188. Martens, K. A. & Almeida, Q. J. Dissociating between sensory and perceptual deficits in PD: More than simply a motor deficit. *Move. Disord.* 27, 387-392 (2012).
189. Pilz, W. *et al.* Oropharyngeal dysphagia in myotonic dystrophy type 1: A systematic review. *Dysphagia* 29, 319-331 (2014).
190. Kang, S. S. *et al.* The association between psychiatric factors and the development of chronic dysphagia after anterior cervical spine surgery. *Eur. Spine J.* 23, 1694-1698 (2014).
191. Perez-Lloret, S. *et al.* Oro-buccal symptoms (dysphagia, dysarthria, and sialorrhea) in patients with Parkinson's disease: Preliminary analysis from the French COPARK cohort. *Eur. J. Neurol.* 19, 28-37 (2012).
192. Lin, B. M. *et al.* The relationship between depressive symptoms, quality of life, and swallowing function in head and neck cancer patients 1 year after definitive therapy. *Laryngoscope* 122, 1518-1525 (2012).
193. Lin, L. C. *et al.* Depressive symptoms in long-term care residents in Taiwan. *J. Adv. Nurs.* 51, 30-37 (2005).
194. Miller, N. *et al.* Swallowing problems in Parkinson disease: frequency and clinical correlates. *J. Neurol. Neurosurg. Psychiatry* 80, 1047-1049 (2009).
195. Airoidi, M. *et al.* Functional and psychological evaluation after flap reconstruction plus radiotherapy in oral cancer. *Head Neck* 33, 458-468 (2011).
196. Thomas, F. J. & Wiles, C. M. Dysphagia and nutritional status in multiple sclerosis. *J. Neurol.* 246, 677-682 (1999).
197. Nogueira, D. & Reis, E. Swallowing disorders in nursing home residents: How can the problem be explained? *Clin. Interventions Aging.* 8, 221-227 (2013).
198. Zhang, L. *et al.* Effect of swallowing training on dysphagia and depression in postoperative tongue cancer patients. *Eur. J. Oncol. Nurs.* 18, 626-629 (2014).
199. Kang, J. H. *et al.* The effect of bedside exercise program on stroke patients with dysphagia. *Ann. Rehabil. Med.* 36, 512-520 (2012).
200. Verdonshot, R. J. *et al.* The relationship between fiberoptic endoscopic evaluation of swallowing outcome and symptoms of anxiety and depression in dysphagic patients. *Laryngoscope* 126, E199-207 (2016).
201. Nguyen, N. P. *et al.* Impact of dysphagia on quality of life after treatment of head-and-neck cancer. *Int. J. Radiat. Oncol. Biol. Phys.* 61, 772-778 (2005).
202. Dum, R. P. *et al.* Motor, cognitive, and affective areas of the cerebral cortex influence the adrenal medulla. *Proc. Natl. Acad. Sci. U S A.* 113, 9922-9927 (2016).
203. Whiting, P. *et al.* The development of QUADAS: A tool for the quality assessment of studies of diagnostic accuracy included in systematic reviews. *BMC Med. Res. Methodol.* 3, 25 (2003).
204. Tubaro, A. Defining overactive bladder: Epidemiology and burden of disease. *Urology* 64 (SUPPL. 1), 2-6 (2004).
205. Milsom, I. *et al.* How widespread are the symptoms of an overactive bladder and how are they managed? A population-based prevalence study. *BJU Int.* 87, 760-766 (2001).
206. Engel, W. J. Uro psychiatry. *Journal - Michigan State Medical Society.* 63, 273-277 (1964).
207. Macaulay, A. J. *et al.* Micturition and the mind: Psychological factors in the aetiology and treatment of urinary symptoms in women. *Br. Med. J.* 294, 540-543 (1987).
208. Cortes E *et al.* The psychology of LUTS: ICI-RS 2011. *Neurourol. Urodyn.* 31, 340-343 (2012).
209. Hirayama, A. *et al.* Risk factors for new-onset overactive bladder in older subjects: results of the Fujiwara-kyo study. *Urology* 80, 71-76 (2012).

210. Nemeroff CB. The neurobiology of depression. *Scientific American* 278, 42-49 (1998).
211. Gordon, J. A. & Hen, R. The serotonergic system and anxiety. *Neuromolecular Med.* 5, 27-40 (2004).
212. Steers, W. Potential targets in the treatment of urinary incontinence. *Rev. Urol.* 3, S19-26 (2001).
213. de Groat, W. C. Influence of central serotonergic mechanisms on lower urinary tract function. *Urology* 59, S1 30-36 (2002).
214. Lee, K. S. *et al.* Alterations in voiding frequency and cystometry in the clomipramine induced model of endogenous depression and reversal with fluoxetine. *J. Urology* 170, 2067-2071 (2003).
215. Steers, W. D. *et al.* Duloxetine compared with placebo for treating women with symptoms of overactive bladder. *BJU Int.* 100, 337-345 (2007).
216. Jost, W. & Marsalek, P. Duloxetine: mechanism of action at the lower urinary tract and Onuf's nucleus. *Clin. Auton. Res.* 14, 220-227 (2004).
217. Arborelius, L. *et al.* The role of corticotropin-releasing factor in depression and anxiety disorders. *J. Endocrinol.* 160, 1-12 (1999).
218. Nemeroff, C. B. Recent advances in the neurobiology of depression. *Psychopharmacol. Bull.* 36, S2 6-23 (2002).
219. Smith, A. L. *et al.* The effects of acute and chronic psychological stress on bladder function in a rodent model. *Urology* 78, 967e1-e7 (2011).
220. Klausner, A. P. *et al.* The role of corticotropin releasing factor and its antagonist, astressin, on micturition in the rat. *Auton. Neurosci.* 123, 26-35 (2005).
221. Wood, S. K. *et al.* Social stress-induced bladder dysfunction: Potential role of corticotropin-releasing factor. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 296, R1671-1678 (2009).
222. Griffiths, D. Imaging bladder sensations. *NeuroUrol. Urodyn.* 26, S899-903 (2007).
223. Griffiths, D. & Tadic, S. D. Bladder control, urgency, and urge incontinence: Evidence from functional brain imaging. *NeuroUrol. Urodyn.* 27, 466-474 (2008).
224. Komesu, Y. M. *et al.* Functional MRI of the Brain in Women with Overactive Bladder: Brain Activation During Urinary Urgency. *Female Pelvic Med. Reconstr. Surg.* 17, 50-54 (2011).
225. Eisenberger, N. I. The neural bases of social pain: evidence for shared representations with physical pain. *Psychosom. Med.* 74, 126-135 (2012).
226. Griffiths, D. Clinical studies of cerebral and urinary tract function in elderly people with urinary incontinence. *Behav. Brain. Res.* 92, 151-155 (1998).
227. Awata, S. *et al.* Regional cerebral blood flow abnormalities in late-life depression: Relation to refractoriness and chronification. *Psychiatry Clin. Neurosci.* 52, 97-105 (1998).
228. Bushnell, M. C. *et al.* Cognitive and emotional control of pain and its disruption in chronic pain. *Nat. Rev. Neurosci.* 14, 502-511 (2013).
229. Russo, S. J. & Nestler, E. J. The brain reward circuitry in mood disorders. *Nat. Rev. Neurosci.* 14, 609-625 (2013).
230. Baliki, M. N. *et al.* Functional reorganization of the default mode network across chronic pain conditions. *PLoS One* 9:e106133 (2014).
231. Eisenberger, N. I. The pain of social disconnection: Examining the shared neural underpinnings of physical and social pain. *Nat. Rev. Neurosci.* 13, 421-434 (2012).
232. Sadler, K. E. & Kolber, B. J. Urine trouble: Alterations in brain function associated with bladder pain. *J. Urology* 196, 24-32 (2016).
233. Chung, M. K. *et al.* The overlap of interstitial cystitis/painful bladder syndrome and overactive bladder. *JSL* 14, 83-90 (2010).
234. Lai, H. H. *et al.* The overlap and distinction of self-reported symptoms between interstitial cystitis/bladder pain syndrome and overactive bladder: A questionnaire based analysis. *J. Urol.* 192, 1679-1685 (2014).
235. Suskind, A. M. *et al.* The prevalence and overlap of interstitial cystitis/bladder pain syndrome and chronic prostatitis/chronic pelvic pain syndrome in men: Results of the RAND Interstitial Cystitis Epidemiology male study. *J. Urol.* 189, 141-145 (2013).
236. Matsumoto, S. *et al.* Relationship between overactive bladder and irritable bowel syndrome: A large-scale Internet survey in Japan using the overactive bladder symptom score and Rome III criteria. *BJU Int.* 111, 647-652 (2013).

237. Matsuzaki, J. *et al.* High frequency of overlap between functional dyspepsia and overactive bladder. *Neurogastroenterol. Motil.* 24, 821-827 (2012).
238. Chelimsky, G. *et al.* Co-morbidities of interstitial cystitis. *Front. Neurosci.* doi:10.3389/fnins.2012.00114 (2012).
239. Fan, Y. H. *et al.* Non-bladder conditions in female Taiwanese patients with interstitial cystitis/hypersensitive bladder syndrome. *Int. J Urol.* 21, 805-809 (2014).
240. Persson, R. *et al.* The relationship between irritable bowel syndrome, functional dyspepsia, chronic fatigue and overactive bladder syndrome: A controlled study 6 years after acute gastrointestinal infection. *BMC Gastroenterol.* 15, 66 (2015).
241. Lai, H. H. *et al.* Polysymptomatic, polysyndromic presentation of patients with urological chronic pelvic pain syndrome. *J. Urol.* 187, 2106-2112 (2012).
242. Fuoco, M. B. *et al.* Multiple sensitivity phenotype in interstitial cystitis/bladder pain syndrome. *Can. Urol. Assoc. J.* 8, 758-761 (2014).
243. Bullones Rodriguez, M. A. *et al.* Evidence for overlap between urological and nonurological unexplained clinical conditions. *J. Urol.* 189, S66-74 (2013).
244. Kanaan, R. A. *et al.* The association or otherwise of the functional somatic syndromes. *Psychosom. Med.* 69, 855-889 (2007).
245. Fink, P. & Schröder, A. One single diagnosis, bodily distress syndrome, succeeded to capture 10 diagnostic categories of functional somatic syndromes and somatoform disorders. *J. Psychosom. Res.* 68, 415-426 (2010).
246. Wessely, S. & White, P. D. There is only one functional syndrome. *Br. J. Psychiatry* 185, 95-96 (2004).
247. Kim, S. E. & Chang, L. Overlap between functional GI disorders and other functional syndromes: What are the underlying mechanisms? *Neurogastroenterol. Motil.* 24, 895-913 (2012).
248. Warren, J. W. *et al.* The number of existing functional somatic syndromes (FSSs) is an important risk factor for new, different FSSs. *J. Psychosom. Res.* 74, 12-17 (2013).
249. Warren, J. W. *et al.* Before the onset of interstitial/bladder pain syndrome, the presence of multiple non-bladder syndromes is strongly associated with a history of multiple surgeries. *J. Psychosom. Res.* 76, 75-79 (2014).
250. Warren, J. W. *et al.* Functional somatic syndromes as risk factors for hysterectomy in early bladder pain syndrome/interstitial cystitis. *J. Psychosom. Res.* 77, 363-367 (2014).
251. Mullins, C. *et al.* Novel research approaches for interstitial cystitis/bladder pain syndrome: Thinking beyond the bladder. *Transl. Androl. Urol.* 4, 524-533 (2015).
252. Drossman, D. A. The functional gastrointestinal disorders and the Rome III process. *Gastroenterology* 130, 1377-1390 (2006).
253. Longstreth, G. F. *et al.* Functional bowel disorders. *Gastroenterology* 130, 1480-1491 (2006).
254. Abrams, P. *et al.* The standardisation of terminology of lower urinary tract function: Report from the standardisation subcommittee of the International Continence Society. *Neurourol. Urodyn.* 21, 167-178 (2002).
255. Fall, M. *et al.* EAU guidelines on chronic pelvic pain. *Eur. Urol.* 46, 681-689 (2004).
256. van de Merwe, J. P. *et al.* Diagnostic criteria, classification, and nomenclature for painful bladder syndrome/interstitial cystitis: An ESSIC proposal. *Eur. Urol.* 53, 60-67 (2008).
257. van Ophoven, A. *et al.* From end-organ disease to a classable bladder pain syndrome: Paradigm shift in the understanding of urological pain syndromes exemplified by the condition currently called interstitial cystitis. *Urologe A.* 48, 152-162 (2009).
258. Fall, M. *et al.* EAU guidelines on chronic pelvic pain. *Eur. Urol.* 57, 35-48 (2010).
259. Engeler, D. S. *et al.* The 2013 EAU guidelines on chronic pelvic pain: is management of chronic pelvic pain a habit, a philosophy, or a science? 10 years of development. *Eur. Urol.* 64, 431-439 (2013).
260. Wesselmann, U. A new paradigm in chronic bladder pain. *J. Pain Palliat. Care Pharmacother.* 28, 406-408 (2014).
261. Twiddy, H. *et al.* The development and delivery of a female chronic pelvic pain management programme: A specialised interdisciplinary approach. *Br. J. Pain.* 9, 233-240 (2015).
262. Hanno, P. M. *et al.* Diagnosis and treatment of interstitial cystitis/bladder pain syndrome: AUA guideline amendment. *J. Urol.* 193, 1545-1553 (2015).

263. Parsons, C. L. The role of a leaky epithelium and potassium in the generation of bladder symptoms in interstitial cystitis/overactive bladder, urethral syndrome, prostatitis and gynaecological chronic pelvic pain. *BJU Int.* 107, 370-375 (2011).
264. Homma, Y. Hypersensitive bladder: A solution to confused terminology and ignorance concerning interstitial cystitis. *Int. J. Urol.* 21, S41-47 (2014).
265. Hurst, R. E. *et al.* Increased bladder permeability in interstitial cystitis/painful bladder syndrome. *Transl. Androl. Urol.* 5, 563-571 (2015).
266. Das, R. *et al.* Dimensions of sensation assessed in urinary urgency: a systematic review. *J. Urol.* 190, 1165-1172 (2013).
267. Juszczak, K. *et al.* Hyperosmolarity alters micturition: a comparison of urinary bladder motor activity in hyperosmolar and cyclophosphamide-induced models of overactive bladder. *Can. J. Physiol. Pharmacol.* 88, 899-906 (2010).
268. Greenwood-van Meerveld, B. *et al.* Mechanisms of visceral organ crosstalk: Importance of alterations in permeability in rodent models. *J. Urol.* 194, 804-811 (2015).
269. Yoshikawa, S. *et al.* Pelvic organ cross-sensitization to enhance bladder and urethral pain behaviors in rats with experimental colitis. *Neuroscience* 284, 422-429 (2015).
270. Valentino, R. J. *et al.* The bladder-brain connection: putative role of corticotropin-releasing factor. *Nat. Rev. Urol.* 8, 19-28 (2011).
271. Martinez-Martinez, L. A. *et al.* Sympathetic nervous system dysfunction in fibromyalgia, chronic fatigue syndrome, irritable bowel syndrome, and interstitial cystitis: A review of case-control studies. *J. Clin. Rheumatol.* 20, 146-150 (2014).
272. Williams, D. P. Effects of chronic pelvic pain on heart rate variability in women. *J. Urol.* 194, 1289-1294 (2015).
273. Hughes, P. A. *et al.* Immune activation in irritable bowel syndrome: Can neuroimmune interactions explain symptoms? *Am. J. Gastroenterol.* 108, 1066-1074 (2013).
274. Cartwright, R. *et al.* Novel biomarkers for overactive bladder. *Nat. Rev. Urol.* 8, 139-145 (2011).
275. Qu, H. C. *et al.* Association between polymorphism of  $\beta$ 3-adrenoceptor gene and overactive bladder: A meta-analysis. *Genet. Mol. Res.* 14, 2495-2501 (2015).
276. Talati, A. *et al.* Panic disorder, social anxiety disorder, and a possible medical syndrome previously linked to chromosome 13. *Biol. Psychiatry* 63, 594-601 (2008).
277. Whiteside, S.A. *et al.* The microbiome of the urinary tract - a role beyond infection. *Nat. Rev. Urol.* 12, 81-90 (2015).
278. Pierce, A. N. & Christianson, J. A. Stress and chronic pelvic pain. *Prog. Mol. Biol. Transl. Sci.* 131, 509-535 (2015).
279. Choung, R. S. *et al.* Psychosocial distress and somatic symptoms in community subjects with irritable bowel syndrome: A psychosocial component is the rule. *Am. J. Gastroenterol.* 104, 1772-1779 (2009).
280. Koloski, N.A. *et al.* Does psychological distress modulate functional gastrointestinal symptoms and health care seeking? *Am. J. Gastroenterol.* 98, 789-797 (2003).
281. Lackner, J. M. *et al.* Testing the sequential model of pain processing in irritable bowel syndrome: A structural equation modeling analysis. *Eur. J. Pain* 9, 207-18 (2005).
282. Koloski, N. A. *et al.* What level of IBS symptoms drives impairment in health-related quality of life in community subjects with irritable bowel syndrome? Are current IBS syndrome thresholds clinically meaningful? *Qual. Life Res.* 21, 829-836 (2012).
283. Link, C. L. *et al.* Is abuse causally related to urologic symptoms? Results from the Boston Area Community Health (BACH) survey. *Eur. Urol.* 52, 397-406 (2007).
284. Rothrock, N. E. *et al.* Stress and symptomatology in patients with interstitial cystitis: A life stress model. *Urology* 57, 422-427 (2001).
285. Hsiao, S. M. *et al.* Psychometric assessment of female overactive bladder syndrome and antimuscarinic-related effects. *Maturitas* 79, 428-434 (2014).
286. Lai, H. H. *et al.* Urological symptoms in a subset of patients with urological chronic pelvic pain syndrome and a polysymptomatic, polysyndromatic pattern of presentation. *J. Urol.* 191, 1802-1807 (2014).
287. Krieger, J. N. *et al.* Relationship between chronic nonurological associated somatic syndromes and symptom severity in urological chronic pelvic pain syndromes: Baseline evaluation of the MAPP study. *J. Urol.* 193, 1254-1262 (2015).

288. Riegel B. *et al.* Assessing psychological factors, social aspects and psychiatric co-morbidity associated with Chronic Prostatitis/Chronic Pelvic Pain Syndrome (CP/CPPS) in men: A systematic review. *J. Psychosom. Res.* 77, 333-350 (2014).
289. olde Hartman, T. C. *et al.* Chronic functional somatic symptoms: A single syndrome? *Br. J. Gen. Pract.* 54, 922-927 (2004).
290. Lackner, J. M. Type, rather than number, of mental physical comorbidities increases the severity of symptoms in patients with irritable bowel syndrome. *Clin. Gastroenterol. Hepatol.* 11, 1147-1157 (2013).
291. Diagnostic and Statistical Manual of Mental Disorders. 5<sup>th</sup> edition. Washington, DC: American Psychiatric Association (2013).
292. The ICD-10 Classification of Mental and Behavioural Disorders: Diagnostic Criteria for Research. World Health Organization, Geneva (1993).
293. Jylhä, P. & Isometsä, E. The relationship of neuroticism and extraversion to symptoms of anxiety and depression in the general population. *Depress. Anxiety* 23, 281-289 (2006).
294. Klein, D. N. *et al.* Personality and depression: Explanatory models and review of the evidence. *Annu. Rev. Clin. Psychol.* 7, 269-295 (2011).
295. Lai, H. H. *et al.* Painful bladder filling and painful urgency are distinct characteristics in men and women with urological chronic pelvic pain syndromes: A MAPP research network study. *J. Urol.* 194, 1634-1641 (2015).
296. Koh, J. S. *et al.* The association of personality trait on treatment outcomes in patients with chronic prostatitis/chronic pelvic pain syndrome: An exploratory study. *J. Psychosom. Res.* 76, 127-133 (2014).
297. Koh, J. S. *et al.* The impact of depression and somatic symptoms on treatment outcomes in patients with chronic prostatitis/chronic pelvic pain syndrome: A preliminary study in a naturalistic treatment setting. *Int. J. Clin. Pract.* 68, 478-485 (2014).
298. Tayama, J. *et al.* Effects of personality traits on the manifestations of irritable bowel syndrome. *Bio. Psycho. Soc. Med.* 6, 20 (2012).
299. Goldstein, B. L. & Klein D. N. A review of selected candidate endophenotypes for depression. *Clin. Psychol. Rev.* 34, 417-27 (2014).
300. Ormel, J. *et al.* Neuroticism and common mental disorders: Meaning and utility of a complex relationship. *Clin. Psychol. Rev.* 33, 686-697 (2013).
301. Muscatello, M. R. *et al.* Role of negative affects in pathophysiology and clinical expression of irritable bowel syndrome. *World J. Gastroenterol.* 20, 7570-7586 (2014).
302. den Boeft, M. *et al.* The association between medically unexplained physical symptoms and health care use over two years and the influence of depressive and anxiety disorders and personality traits: A longitudinal study. *BMC Health Serv. Res.* doi: 10.1186/s12913-016-1332-7 (2016).
303. Kroenke, K. & Spitzer, R. L. Gender differences in the reporting of physical and somatoform symptoms. *Psychosom. Med.* 60, 150-155 (1998).
304. Goodwin, R. D. & Gotlib, I. H. Gender differences in depression: The role of personality factors. *Psychiatry Res.* 126, 135-142 (2004).
305. Koenig, H. G. Depression in hospitalized older patients with congestive heart failure. *Gen. Hosp. Psychiatry* 20, 29-43 (1998).
306. Strik, J. J. *et al.* One-year cumulative incidence of depression following myocardial infarction and impact on cardiac outcome. *J. Psychosom. Res.* 56, 59-66 (2004).
307. Fishbain, D. A. *et al.* Chronic pain-associated depression: Antecedent or consequence of chronic pain? A review. *Clin. J. Pain* 13, 116-137 (1997).
308. Bair, M. J. *et al.* Anxiety but not Social Stressors Predict 12-Month Depression and Pain Severity. *Clin. J. Pain* 29, 95-101 (2013).
309. Gerrits, M. M. *et al.* Pain and the onset of depressive and anxiety disorders. *Pain* 155, 53-59 (2014).
310. Kroenke, K, *et al.* Reciprocal Relationship between Pain and Depression: A 12-month longitudinal analysis in Primary Care. *J. Pain* 12, 964-973 (2011).
311. Koloski, N. A. *et al.* The brain-gut pathway in functional gastrointestinal disorders is bidirectional: A 12-year prospective population-based study. *Gut* 61, 1284-1290 (2012).
312. Pinto-Sanchez, M. I. *et al.* Anxiety and depression increase in a stepwise manner in parallel with multiple FGIDs and symptom severity and frequency. *Am. J. Gastroenterol.* 110, 1038-1048 (2015).

313. Lai, H. *et al.* Correlation between psychological stress levels and the severity of overactive bladder symptoms. *BMC Urology* 15, 14 (2015).
314. Yunus, M. B. Fibromyalgia and overlapping disorders: The unifying concept of central sensitivity syndromes. *Semin. Arthritis Rheum.* 36, 339-356 (2007).
315. Drossman, D. A. *et al.* Severity in irritable bowel syndrome: A Rome foundation working team report. *Am J. Gastroenterol.* 106, 1749-59 (2011).
316. Drossman, D. A. Do psychosocial factors define symptom severity and patient status in irritable bowel syndrome? *Am. J. Med.* 107, 41S-50 (1999).
317. Surdea-Blaga, T. *et al.* Psychosocial determinants of irritable bowel syndrome. *World J. Gastroenterol.* 18, 616-626 (2012).
318. Costa, P. T. & McCrae, R. R. NEO PI-R professional manual. Odessa, FL. Psychological Assessment Resources, Inc. (1992)
319. Hazlett-Stevens, H. *et al.* Prevalence of irritable bowel syndrome among university students: The roles of worry, neuroticism, anxiety sensitivity and visceral anxiety. *J. Psychosom. Res.* 55, 501-505 (2003).
320. Farnam, A. *et al.* Personality factors and profiles in variants of irritable bowel syndrome. *World J. Gastroenterol.* 13, 6414-6418 (2007).
321. van Tilburg, M. A. *et al.* Which psychological factors exacerbate irritable bowel syndrome? Development of a comprehensive model. *J. Psychosom. Res.* 74, 486-492 (2013).
322. Sullivan, M. J. *et al.* Theoretical perspectives on the relation between catastrophizing and pain. *Clin. J. Pain* 17, 52-64 (2001).
323. Lackner, J. M. *et al.* Depression and abdominal pain in IBS patients: the mediating role of catastrophizing. *Psychosom. Med.* 66, 435-441 (2004).
324. Lackner, J. M. *et al.* Patient reported outcomes for irritable bowel syndrome are associated with patients' severity ratings of gastrointestinal symptoms and psychological factors. *Clin. Gastroenterol. Hepatol.* 9, 957-964 (2011).
325. Spiller, R. Postinfectious functional dyspepsia and postinfectious irritable bowel syndrome: Different symptoms but similar risk factors. *Gastroenterology* 138, 1660-1663 (2010).
326. Rudick, C. N. *et al.* O-antigen modulates infection-induced pain states. *PLoS One* 7, e1273 (2012).
327. O'Brien, V. P. *et al.* A mucosal imprint left by prior *Escherichia coli* bladder infection sensitizes to recurrent disease. *Nat. Microbiol.* 2: 16196 (2016).
328. Rosen, J. M. & Klumpp, D. J. Mechanisms of pain from urinary tract infection. *Int. J. Urol.* 21 (Suppl. 1), 26-32 (2014).
329. Janssens, K. A. *et al.* Mood and anxiety disorders in chronic fatigue syndrome, fibromyalgia, and irritable bowel syndrome: Results from the LifeLines cohort study. *Psychosom. Med.* 77, 449-457 (2015).
330. Thijssen, A. Y. *et al.* Dysfunctional cognitions, anxiety and depression in irritable bowel syndrome. *J. Clin. Gastroenterol.* 44, e236-241 (2010).
331. El-Serag, H. B. *et al.* Systematic review: Natural history of irritable bowel syndrome. *Aliment. Pharmacol. Ther.* 19, 861-870 (2004).
332. Giarensis, I. & Cardozo L. Management of refractory overactive bladder. *Minerva Ginecol.* 65, 41-52 (2013).
333. Marshall, J. K. *et al.* Eight year prognosis of post infectious irritable bowel syndrome following waterborne bacterial dysentery. *Gut* 59, 605-611 (2010).
334. Berghmans, B. *et al.* Prevalence and triage of first-contact complaints on pelvic floor dysfunctions in male patients referred to a Pelvic Care Centre. *Neurourol. Urodyn.* 35, 487-491 (2016).
335. Filipetto, F. A. *et al.* The patient perspective on overactive bladder: A mixed-methods needs assessment. *BMC Fam. Pract.* doi: 10.1186/1471-2296-15-96 (2014).
336. Bosch, P. C. & Bosch, D. C. Treating interstitial cystitis/bladder pain syndrome as a chronic disease. *Rev. Urol.* 16, 83-87 (2014).
337. Mujagic, Z. *et al.* Systematic review: instruments to assess abdominal pain in irritable bowel syndrome. *Aliment. Pharmacol. Ther.* 42, 1064-1081 (2015).
338. Myin-Germeys, I. Experience sampling research in psychopathology: Opening the black box of daily life. *Psychol. Med.* 39, 1533-1547 (2009).
339. van Os, J. *et al.* Testing an mHealth momentary assessment Routine Outcome Monitoring application: A focus on restoration of daily life positive mood states. *PLoS One* 9:e115254 (2014).



340. Wichers, M. *et al.* Momentary assessment technology as a tool to help patients with depression help themselves. *Acta Psychiatr. Scand.* 124, 262-272 (2011).
341. Myin-Germeys, I. *et al.* Emotional reactivity to daily life stress in psychosis and affective disorder: An experience sampling study. *Acta Psychiatr. Scand.* 107, 124-131 (2003).
342. van Os, J. *et al.* The experience sampling method as an mHealth tool to support self-monitoring, self-insight, and personalized care in clinical practice. *Depress Anxiety* doi: 10.1002/da.22647 (2017).
343. Häuser, W. *et al.* Construct validity and clinical utility of current research criteria of DSM-5 somatic symptom disorder diagnosis in patients with fibromyalgia syndrome. *J. Psychosom. Res.* 78, 546-552 (2015).
344. Levenson, J. L. Essentials of Psychosomatic Medicine. *American Psychiatric Press Inc.* ISBN 978-1-58562-246-247 (2006).
345. Wise, T. N. Update on consultation-liaison psychiatry (psychosomatic medicine). *Curr. Opin. Psychiatry* 21,196-200 (2008).
346. Nusslock, R. & Miller, G. E. Early-life adversity and physical and emotional health across the lifespan: A neuroimmune network hypothesis. *Biol. Psychiatry* Pii:S0006-3223(15)00466-7 (2015).
347. Barnes, J. *et al.* Genetic contributions of inflammation to depression. *Neuropsychopharmacology* 42, 81-98 (2017).
348. Plummer, J. T. *et al.* The genetic intersection of neurodevelopmental disorders and shared medical comorbidities – relations that translate from bench to bedside. *Front. Psychiatry* 7, 142 (2016).
349. Simons, L. *et al.* Psychological processing in chronic pain: A neural systems approach. *Neurosci. Biobehav. Rev.* 39, 61-78 (2014).
350. Miller, B. J. & Goldsmith, D. R. Towards an immunophenotype of schizophrenia: Progress, potential mechanisms, and future directions. *Neuropsychopharmacology* 42, 299-317 (2017).
351. Shefer, G. *et al.* Diagnostic overshadowing and other challenges involved in the diagnostic process of patients with mental illness who present in emergency departments with physical symptoms - a qualitative study. *PLoS One* 9, e111682 (2014).
352. Shefer, G. *et al.* Improving the diagnosis of physical illness in patients with mental illness who present in emergency departments: consensus study. *J. Psychosom. Res.* 78, 346-351 (2015).
353. Burian, R. *et al.* Crossing the bridge - a prospective comparative study of the effect of communication between a hospital based consultation-liaison service and primary care on general practitioners' concordance with consultation-liaison psychiatrists' recommendations. *J. Psychosom. Res.* 86, 53-59 (2016).
354. Lücke, C. *et al.* A comparison of two psychiatric service approaches: findings from the Consultation vs. Liaison Psychiatry-Study. *BMC Psychiatry* 17: 8 (2017).
355. Brownell, A. K. *et al.* Clinical practitioners' view on the management of patients with medically unexplained physical symptoms (MUPS): A qualitative study. *BMJ Open* 6: e012379 (2016).
356. Sharpe, M. A collaborative care approach delivering treatment to patients with depression comorbid with diabetes or cardiovascular disease achieves significant but small improvements over usual care in depression and patient satisfaction. Comment in *Evid. Based Ment. Health* 18, 122 (2015).
357. Barnett, K. *et al.* Epidemiology of multimorbidity and implications for health care, research, and medical education: A cross-sectional study. *Lancet* 380, 37-43 (2012).
358. Naylor, C. *et al.* Long-term conditions and mental health: The cost of co-morbidities. London: The King's Fund (2012).
359. Kendler, K. S. Causal inference in psychiatric epidemiology. *JAMA Psychiatry* 74, 561-562 (2017).
360. Mujagic, Z. *et al.* The Experience Sampling Method - a new digital tool for momentary symptom assessment in IBS: an exploratory study. *Neurogastroenterol. Motil.* 27, 1295-1302 (2015).
361. Katon, W. J. & Unützer, J. Health reform and the Affordable Care Act: the importance of mental health treatment to achieving the triple aim. *J. Psychosom. Res.* 74, 533-537 (2013).
362. Kessler, R. C. *et al.* Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the national comorbidity survey replication. *Arch. Gen. Psychiatry* 62, 593-602 (2005).
363. Lovell RM, Ford AC. Global prevalence of and risk factors for irritable bowel syndrome: A meta-analysis. *Clin. Gastroenterol. Hepatol.* 10, 712-721 (2012).
364. Milsom, I. *et al.* Global prevalence and economic burden of urgency urinary incontinence: A systematic review. *Eur. Urol.* 65, 79-95 (2014).

365. Lackner, J. M. *et al.* The impact of physical complaints, social environment, and physical functioning on IBS patients' health perception: looking beyond GI symptom severity. *Am. J. Gastroenterol.* 109, 224-233 (2014).
366. Kessler, R. C. *et al.* Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the national comorbidity survey replication. *Arch. Gen. Psychiatry* 62, 593-602 (2005).
367. Cole J. A. *et al.* Migraine, fibromyalgia and depression among people with IBS: A prevalence study. *BMC Gastroenterology* 6, 26 (2006).
368. Clemens, J. Q. *et al.* Temporal ordering of interstitial cystitis/bladder pain syndrome and non-bladder conditions. *Urology.* 80, 1227-1231 (2012).
369. Nickel, J. C. *et al.* Interstitial cystitis/painful bladder syndrome and associated medical conditions with an emphasis on irritable bowel syndrome, fibromyalgia and chronic fatigue syndrome. *J. Urol.* 184, 1358-1363 (2010).
370. Lutgendorf, S. K. *et al.* Stress and symptomatology in patients with interstitial cystitis: A laboratory stress model. *J. Urol.* 164, 1265-1269 (2000).
371. Nickel, J. C. *et al.* Clinical and psychological parameters associated with pain pattern phenotypes in women with interstitial cystitis/bladder pain syndrome. *J. Urol.* 193, 138-144 (2015).
372. Chung, K. H. *et al.* Bladder pain syndrome/interstitial cystitis is associated with anxiety disorder. *Neurourol. Urodyn.* 33, 101-105 (2014).
373. Clemens, J. Q. *et al.* Temporal ordering of interstitial cystitis/bladder pain syndrome and non-bladder conditions. *Urology.* 80, 1227-1231 (2012).
374. Nickel, J. C. *et al.* Interstitial cystitis/painful bladder syndrome and associated medical conditions with an emphasis on irritable bowel syndrome, fibromyalgia and chronic fatigue syndrome. *J. Urol.* 184, 1358-1363 (2010).
375. Leue, C. Organisch begründete psychische Erkrankungen - am Beispiel des Delirs. *Uexküll: Psychosomatische Medizin – Theoretische Modelle und klinische Praxis.* 8. Auflage. Kapitel 99;1123-1130 (2017).
376. Hoogervorst-Schilp, J. Excess length of stay and economic consequences of adverse events in Dutch hospital patients. *BMC Health Serv. Res.* 15:531 (2015).
377. Rivara, F. P. *et al.* The effects of alcohol abuse on readmission for trauma. *JAMA* 270, 1962-1964 (1993).
378. Hannan, E. L. *et al.* Predictors of readmission for complications of coronary artery bypass graft surgery. *JAMA* 290, 773-780 (2003).
379. Heslin, K. C. *et al.* Hospitalizations involving mental and substance use disorders among adults, 2012. *Healthcare cost and utilization project (HCUP), Statistical brief* 191, (2015).
380. Marks, E. Complexity science and the readmission dilemma. *JAMA Intern. Med.* 173, 629-631 (2013).
381. Steiner, C. A. *et al.* Trends and projections in hospital stays for adults with multiple chronic conditions, 2003-2014. *Healthcare cost and utilization project (HCUP), Statistical brief* 183, (2014).
382. Barrett, M. L. *et al.* All-cause readmissions by payer and age, 2009-2013. *Healthcare cost and utilization project (HCUP), Statistical brief* 199, (2015).
383. Heslin, K. C. & Weiss, A. J. Hospital readmissions involving psychiatric disorders, 2012. *Healthcare cost and utilization project (HCUP), Statistical brief* 189, (2015).
384. Vigod, S. N. *et al.* Transitional interventions to reduce early psychiatric readmissions in adults: Systematic review. *Br. J. Psychiatry* 202, 187-194 (2013).
385. Vaduganathan, M. *et al.* Thirty-day readmissions: The clock is ticking. *JAMA* 309, 345-346 (2013).
386. Donzé, J. *et al.* Causes and patterns of readmissions in patients with common comorbidities: Retrospective cohort study. *BMJ* 347, f7171 (2013).
387. Fabbian, F. *et al.* The crucial factor of hospital readmissions: A retrospective cohort study of patients evaluated in the emergency department and admitted to the department of medicine of a general hospital in Italy. *Eur. J. Med. Res.* 20, 6 (2015).
388. Scott, I. A. *et al.* Quality of care factors associated with unplanned readmissions of older medical patients: A case-control study. *Intern. Med. J.* 44, 161-170 (2014).
389. Kangovi, S. & Grande, D. Hospital readmissions – not just a measure of quality. *JAMA* 306, 1796-1797 (2011).
390. Strunin, L. *et al.* Understanding rehospitalization risk. *J. Hosp. Med.* 2, 297-304 (2007).

391. Medicaid Access Study Group. Access of Medicaid recipients to outpatient care. *N. Eng. J. Med.* 330, 1426-1430 (1994).
392. Williams, M. V. A requirement to reduce readmissions: Take care of the patient, not just the disease. *JAMA* 309, 394-396 (2013).
393. Milstein, A. & Shortell, S. Innovations in care delivery to slow growth of US health spending. *JAMA* 308, 1439-1440 (2012).
394. Jenq, G. & Tinetti M. E. The journey across the health care (dis) continuum for vulnerable patients. *JAMA* 307, 2157-2158 (2012).
396. McCarthy, D. *et al.* Recasting readmissions by placing the hospital role in community context. *JAMA* 309, 351-352 (2013).
397. Calvillo-King, L. *et al.* Impact of social factors on risk of readmission or mortality in pneumonia and heart failure. *J. Gen. Intern. Med.* 28, 269-282 (2013).
397. Goekoop, R. & Goekoop, J. G. A network view on psychiatric disorders: Network clusters of symptoms as elementary syndromes of psychopathology. *PLoS One* 9, e112734 (2014).
398. van Rooijen, G. *et al.* A state-independent network of depressive, negative and positive symptoms in male patients with schizophrenia spectrum disorders. *Schizophr. Res.* pii: S0920-9964(17)30446-2 (2017).
399. Grupp, H. *et al.* Excess costs from functional somatic syndromes in Germany – an analysis using entropy balancing. *J. Psychosom. Res.* 97, 52-57 (2017).
400. Baumeister, H. *et al.* Direct and indirect costs with chronic back pain and comorbid mental disorders – a systematic review. *J. Psychosom. Res.* 73, 79-85 (2012).
401. Gawronski, K. A. *et al.* Potentially traumatic events and serious life stressors are prospectively associated with frequency of doctor visits and overnight hospital visits. *J. Psychosom. Res.* 77, 90-96 (2014).
402. van Gils, A. *et al.* Individual variation in the temporal relationships between stress and functional somatic symptoms. *J. Psychosom. Res.* 77, 34-39 (2014).
403. Sousa, N. The dynamics of the stress neuromatrix. *Mol. Psychiatry* 21, 302-312 (2016).
404. Williams, L. J. *et al.* Pain and the relationship with mood and anxiety disorders and psychological symptoms. *J. Psychosom. Res.* 72, 452-456 (2012).
405. Jaracz, J. *et al.* Unexplained painful physical symptoms in patients with major depressive disorder: Prevalence, pathophysiology and management. *CNS Drugs* 30, 293-304 (2016).
406. Dijkstra-Kersten, S. M. *et al.* Longitudinal associations of multiple physical symptoms with recurrence of depressive and anxiety disorders. *J. Psychosom. Res.* 97, 96-101 (2017).
407. Huijbregts, K. M. *et al.* Negative association of concomitant physical symptoms with the course of major depressive disorder: A systematic review. *J. Psychosom. Res.* 68, 511-519 (2010).
408. Auerbach, A. D. *et al.* Preventability and causes of readmissions in a national cohort of general medicine patients. *JAMA Intern. Med.* 176, 484-493 (2016).
409. van Galen, L. S. *et al.* Patients' and providers' perception of the preventability of hospital readmissions: A prospective, observational study in four European countries. *BMJ Qual. Saf.* pii: bmjqs-2017-006645 (2017).
410. McAndrew, L. M. *et al.* High healthcare utilization near the onset of medically unexplained symptoms. *J. Psychosom. Res.* 98, 98-105 (2017).
411. de Jong, M. J. *et al.* Telemedicine for management of inflammatory bowel disease (myIBDcoach): A pragmatic, multicentre, randomised controlled trial. *Lancet* 390, 959-968 (2017).
412. van Os, J. *et al.* The experience sampling method as an mHealth tool to support self-monitoring, self-insight, and personalized health care in clinical practice. *Depress. Anxiety* 34, 481-493 (2017).