

type I at the other. Mixed states can occur at any point along this scale and hence what they signify remains unclear. Clinically, the admixture of symptoms seen in mixed states has been conceptualised variously as the transition from one pole of bipolarity to the other, rapid cycling in extremis, or the result of treatment with antidepressants. In reality, discrete but overlapping disease entities can exist along a scale: hence both possibilities (categorical and dimensional) are potentially useful, and the occurrence of mixed states indicates, at the very least, that our existing models of mood disorders, and in particular bipolarity, are incomplete⁶ and perhaps inaccurate.

Despite the prevalence of mixed states (roughly 20%), research into the efficacy of treatments for robustly diagnosed mixed states is remarkably scarce.⁷ The consequence is that assignment of an MxFS to a diagnosis of depression or mania or hypomania might not meaningfully change the treatment of the primary episode. Indeed, most existing treatment guidelines do not make any specific recommendations for treatment of mixed states, even though empirically the idea that mixed presentation increases the likelihood of a poorer treatment outcome is widely accepted.⁸ A further consideration in the treatment of mixed states is the risk that a switch in mood state might be triggered, or that mixed state symptoms could be exacerbated. Such concerns are indicative of our inadequate knowledge of bipolar pathophysiology and the mechanisms by which drugs used to treat the illness achieve their effects.⁹

Gaps in our understanding should surely prompt further research for external validators of poorly defined diagnostic entities, such as mixed states, rather than further arbitrary loosening of the phenomenology of

bipolar disorder. The present mix of features in bipolar disorder that will be specified by the new classification system will produce a myriad of manifestations and further complicate an already confusing diagnostic landscape (figure).¹⁰ The imprecise DSM-5 MxFS will probably increase the occurrence of mixed states and further obscure the boundary between major depression and bipolar disorder. Clinically, this outcome will create additional diagnostic uncertainty in the minds of clinicians managing patients with bipolarity, prompting the question: who is in a mixed state?

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Fast-track hip and knee arthroplasty

Fast-track surgery or enhanced postoperative recovery programmes have evolved during the past 15 years and have proven effective across a range of procedures in terms of reductions in length of hospital stay, morbidity, and convalescence, without an increase in readmission rates or safety issues.^{1,2} Most data have come from colorectal procedures, including physiological data for preservation of muscle mass and function and cardiopulmonary response to exercise.^{1,2}

Total hip and knee arthroplasties are common major procedures that are often done in older patients with complex comorbidities. Although reductions in length of hospital stay from 4–10 days to about 2–4 days with discharge to home have been reported,^{3–7} including from unselected cohort studies,^{3,4,7} large-scale regional and national data from European countries have often shown a length of stay between 6 and 11 days, which has implications for health-care costs. Recent efforts to

implement fast-track total hip and knee arthroplasty programmes on a large scale have successfully reduced hospital stays to **about 5 days**.⁸ However, data for length of stay need to be **interpreted carefully**, since patients in some places might be **discharged** to **rehabilitation** institutions directly from hospital.⁹ For future progress, the issue is to identify the factors that cause patients to remain in hospital.¹³ The main aim of fast-track surgery is to enhance recovery and reduce morbidity. If successful, secondary benefits will include reductions in length of stay, convalescence, and costs.^{1,6}

Effective postoperative pain management is necessary for early recovery after total hip or knee arthroplasties and other procedures,^{1,3,10} and **evidence-based** techniques include **spinal** anaesthesia, **peripheral** nerve blocks, and **non-steroidal** anti-inflammatory drugs **combined** with **paracetamol**. Simple, intraoperative, high-volume local anaesthetic wound infiltration has proven effective for early pain relief after total knee arthroplasty, but **not** after total hip arthroplasty.¹¹ Although **single-dose** or **continuous** **peripheral** nerve blocks can optimise **analgesia**, the risk of muscle **weakness** and **falls** might preclude their continued use. Future improvements could include the use of **preoperative** **high-dose** **glucocorticoids**,¹² **gabapentinoids**, **duloxetine**, and **ketamine**.¹⁰

A focus on the **pathogenesis** of **muscle weakness** is also **needed**,³ since **quadriceps** **strength** is **reduced** by **30% or 80%** soon after total **hip** or **knee** arthroplasty, respectively. Data from randomised trials have cast **doubt** on the **conventional** use of **physiotherapy** after these procedures, but most of these studies have **initiated** **physiotherapy** **weeks** after the operation.¹³ Future efforts should instead **focus** on early **postoperative** muscle **strength** **training**.¹³ Since **early** **mobilisation** is **essential** to **success**, **early** **dizziness** and postoperative **orthostatic intolerance** due to **reduced** peripheral **vascular** **contraction** when a patient is in an **upright** position¹⁴ should be investigated to identify causal **mechanisms** and **strategies** for prevention.

Preoperative anaemia is common in older patients who undergo total hip or knee arthroplasties and is a risk factor for postoperative morbidity.¹⁵ Preoperative anaemia is aggravated by perioperative blood loss, but treatment with **transfusions** can carry a **risk** itself. Algorithms have been made available for detection, assessment, and management of perioperative anaemia



during these procedures, which include treatment with iron in iron deficiency, treatment with erythropoiesis-stimulating agents, and strategies to reduce blood loss.¹⁵ However, further **assessment** of **anaemia-associated** **functional** **outcomes** in fast-track total hip and knee arthroplasties is needed, since **previous** **data** are based on **long** hospital stays and convalescence.

Total hip and knee arthroplasties carry a risk of thromboembolic complications and have been used as standard surgical models to show the need for **extended** **thromboprophylaxis** for **10–35** days postoperatively. Although the data from randomised trials are conclusive, these data have come from **industry-sponsored** trials with **long** hospital stays (longer than 7 days), despite postoperative immobilisation being a key risk factor for thromboembolism. Recent large-scale, consecutive cohort data from fast-track total hip and knee arthroplasties with lengths of stay of about **3** days suggest that **thromboembolic** **prophylaxis** might **not** be **needed** beyond the **short** **period** of **hospitalisation**.¹⁶ Such results have major economic implications, and suggest the need for large-scale randomised trials or detailed cohort studies to assess the need for extended prophylaxis in these fast-track procedures, and to identify those high-risk patients who will continue to need standard extended prophylaxis.

Postoperative **delirium** and **cognitive dysfunction** are well documented adverse sequelae of major surgery, including total hip and knee arthroplasties. However,

all data for these sequelae come from surgery with long postoperative hospital stays. These problems might be caused by pain, opioid use, sleep disturbances, and the inflammatory surgical stress response—all of which are to some extent interrelated.¹⁷ Data from 220 fast-track total hip and knee arthroplasties with **opioid-sparing multimodal** analgesia and a mean length of stay of **2.7** days showed **no occurrences** (95% CI 0.0–1.6%) of **delirium** in the 2 weeks after surgery,¹⁴ which could potentially have major implications for patient care and the costs of these procedures.

Total hip and knee arthroplasties with conventional care are followed by a risk of morbidity and mortality, especially in preoperative high-risk patients.¹⁸ Since all previously established risk indices have been assessed with traditional care principles, including long lengths of stay,¹⁸ large-scale outcome studies in high-risk patients (defined by tobacco and alcohol use, diabetes, cardiopulmonary and cerebral comorbidity, psychosocial risk factors, etc) who undergo fast-track procedures are needed.^{4,7}

Although many data have been available for fast-track surgery since its development in the early 1990s, implementation of these findings into clinical practice has generally been **slow**.^{1,2,8,18} Difficulties for widespread implementation include the diversity of hospital settings, inadequate staffing of wards, use of opioid-based analgesia regimens, insufficient postoperative mobilisation of patients, absence of well defined discharge criteria, and suboptimum preoperative patient information. Consequently, fast-track programmes include a multidisciplinary collaboration (anaesthesiologists, surgeons, nurses, and physiotherapists), who come to a general agreement on defined evidence-based perioperative care principles, monitoring of data, and adjustment of the programme on the basis of scientific evidence.^{3–5,7}

Despite issues with implementation, the future for patients who undergo total hip and knee arthroplasties could be bright—even for older, high-risk patients. Improved non-opioid analgesic techniques, together with an improved understanding of **early loss** of **muscle** function, **orthostatic** intolerance, perioperative blood management, mechanisms of postoperative **delirium** and cognitive dysfunction, and the need for **thromboembolic** prophylaxis could result in reduction of postoperative hospital stay **to 1–2 days** with

discharge to home. Such data from fast-track total hip and knee arthroplasties might also be transferable to other major surgical procedures with the same outcome issues.

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