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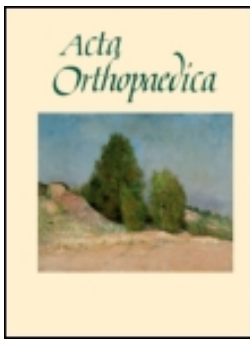
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# Psychiatric disease as a risk factor in fast-track hip and knee replacement

## An overview of the literature

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**Abstract** — Recent studies suggest that patients with psychiatric disorders tend to do worse than patients without a psychiatric diagnosis when undergoing total hip arthroplasty (THA) or total knee arthroplasty (TKA). Whether this is due to their psychiatric condition, pharmacological treatment, a combination of the two, or something else has not been thoroughly analyzed—and there are no internationally accepted guidelines for perioperative management of psychiatric patients. This overview summarizes our current knowledge on perioperative risks in patients with preoperative psychiatric disorders and the possible role of psychotropic drugs in the perioperative course. This will be useful when planning future strategies for improvement of surgical outcome following hip and knee arthroplasty.

Preoperative prediction of surgical risk is essential in order to apply strategies for reduction of postoperative morbidity and convalescence. The concept of fast-track surgery has evolved across various procedures including hip and knee replacement (Kehlet 2013), and has repeatedly been demonstrated to reduce length of hospital stay and morbidity (Kehlet 2013, Khan et al. 2014). It may therefore be questioned whether classical preoperative risk factors (Kehlet and Mythen 2011) are still appropriate when a fast-track care program has been initiated. Thus, recent studies on fast-track hip and knee replacement have suggested that preoperative functional status, cardiopulmonary disease, smoking and alcohol use, and diabetes may now have less of an effect on outcome than previously believed (Jørgensen and Kehlet 2013, Holm et al. 2014, Jørgensen et al. 2015A). In most preoperative risk indices, psychiatric conditions and diseases and also the use of psychopharmacological

drug treatment are rarely taken account of. This may be due to a lack of data, except in patients with serious mental illness (Huysse et al. 2006, Copeland et al. 2008, Bot et al. 2014, Menendez et al. 2014). Some large retrospective database studies in hip and knee arthroplasty have shown conflicting results (Stundner et al. 2013, Buller et al. 2015). In contrast, a recent large prospective study has suggested that psychiatric disorders and the use of psychopharmacological treatment may be more important risk factors in fast-track hip and knee arthroplasty than conventional risk factors by prolonging length of stay (LOS), re-admissions, and morbidity (Jørgensen et al. 2015B). Given the well-established high incidence of psychiatric disease including depression, bipolar disorders, schizophrenia, and anxiety (Olsen et al. 2004, Somers et al. 2006, Clemente et al. 2015), concentrating more on perioperative management of psychiatric patients is both relevant and timely. For this reason, we present a narrative overview of the current state of knowledge concerning psychiatric disease and psychopharmacological therapy as risk factors in fast-track hip and knee replacement. We provide an update on the specific role of psychiatric disease and the role of the effects of psychotropic drugs and any side effects in relation to the perioperative period. Secondly, we outline strategies for future research and clinical practice.

### Psychotropic drugs

Distinction between the psychiatric disease itself and the side effects of psychotropic drugs is a challenge when evaluating perioperative outcomes, raising the question of the relative importance of disease-related factors and drug-related factors and their independent effects on surgical outcome. Use of psychopharmacological drugs was prevalent in about 12% of a

recent Danish cohort for hip and knee arthroplasty (Jørgensen et al. 2015B), but this is seldom considered in preoperative assessment. Furthermore, there are no evidence-based guidelines for psychotropic drugs in the perioperative period, and there is little documentation (Huysse et al. 2006, Strauss 2014). Few studies have focused on the drug-related effects, although some authors have suggested reasonable perioperative drug management strategies (Kudoh 2005, Huysse et al. 2006, Attri et al. 2012, Strauss 2014). Although generally inconclusive, such studies have highlighted the complex and multidisciplinary decision-making process when administering psychotropics perioperatively.

Distinguishing between the effects of psychotropic drugs and the psychiatric disease itself is difficult, even in non-surgical psychiatric patients, as several common postoperative outcome measures (e.g. falls and gastrointestinal bleeding) are already over-represented in patients treated with selective serotonin re-uptake inhibitors (SSRIs) in general (Coupland et al. 2011). In fact, a recent review has questioned the beneficial effects of long-term use of psychotropics altogether (Gotzsche et al. 2015)

In addition, factors such as the extent of surgery, anesthesia, the direct and indirect effects of psychotropics, the risk of withdrawal symptoms, and the risk of psychiatric relapse are worth considering when deciding whether or not to discontinue any psychotropic drug treatment preoperatively (Attri et al. 2012). However, some drugs have been given more attention than others. The SSRIs, which are some of the most common drugs for treating depression and anxiety, have been under scrutiny for their antiplatelet activity. Several studies have indicated that SSRIs enhance the risk of perioperative bleeding, most notably gastrointestinal bleeding related to mucosal injury (Looper 2007, Andrade et al. 2010, Yamamoto et al. 2010, Coupland et al. 2011). Increased perioperative bleeding has also been demonstrated in orthopedic patients treated with SSRIs (Movig et al. 2003, van Haelst et al. 2010), although the clinical relevance is uncertain (Shepherd et al. 2015). Generally, preoperative discontinuation of SSRIs is not recommended—due to risk of discontinuation syndrome and relapse (Huysse et al. 2006, van Haelst et al. 2010, Attri et al. 2012). Study results are conflicting regarding perioperative management of tricyclic anti-depressants (TCAs) (Huysse et al. 2006, Attri et al. 2012, Strauss 2014), but there is agreement that monoamine oxidase inhibitors (MAOIs) can be continued throughout the perioperative period. Lithium, which is also a mood-stabilizing drug used in the treatment of depression and bipolar disorder, has some adverse effects on the kidney and therefore poses a risk in the perioperative period. Routine discontinuation is therefore recommended before surgery (Huysse et al. 2006, Attri et al. 2012). Regarding anti-psychotics, the benefits of continuing outweigh the risks and routine discontinuation is not recommended (Kudoh 2005, Attri et al. 2012, Strauss 2014).

### **Patient- and disease-related factors**

Factors that relate to the patient's psychiatric status have been shown to affect surgical outcome (Bressi et al. 2006, Abrams et al. 2010, Maeda et al. 2014). A negative association has been found for numerous outcomes (see below) and psychiatric disease has been recognized as being an independent risk factor in perioperative management (Bryson and Kellner 2014).

Importantly, this high-risk population already has a significantly shorter life expectancy (Roshanaei-Moghaddam and Katon 2009, Tiihonen et al. 2009, Laursen 2011, Chesney et al. 2014, Ringen et al. 2014, Kessing et al. 2015), except for those with anxiety (Saeed Mirza et al. 2015), mainly due to the high prevalence of concomitant physical comorbidity (Correll et al. 2015). Poor lifestyle choices and disparities in access to, utilization of, and provision of healthcare have been pointed out as primary causes (De Hert et al. 2011).

Poorer outcomes may also apply to hip and knee arthroplasty patients with psychiatric comorbidity. Reports on increased LOS, non-routine discharge, perioperative morbidity, periprosthetic infection rate, mortality rate, surgery-related re-admission rate, risk of falling, and increased perioperative bleeding (van Haelst et al. 2010, Bozic et al. 2012B, Stundner et al. 2013, Buller et al. 2015, Jørgensen et al. 2015B) are all causes for concern. Given the relatively large physical comorbidity burden of these patients, suboptimal outcomes may be expected. One large prospective study has shown a significant increase in perioperative morbidity, surgery-related 90-day re-admissions, and falling—after adjusting for various established confounders (Jørgensen et al. 2015B). Furthermore, all psychopharmacological subgroups had an equal effect on the above-mentioned surgical outcomes, thus suggesting that SSRIs, other anti-depressants, and anti-psychotics are equivalent in this respect. One alternative is that the psychiatric disease itself is fully or partly responsible for the suboptimal surgical outcomes.

### **Patient-reported outcome measures (PROMs)**

Studies have suggested that between 11% and 20% of patients who undergo hip or knee arthroplasty are dissatisfied with regard to pain relief, limited function, or the overall outcome (Rolfson et al. 2011, Drexler et al. 2013, Dunbar et al. 2013, Nam et al. 2014). This is based on health reports given directly by the patients involved in the studies with no intermediate interpretations from others—so-called patient-reported outcome measures (PROMs) (Rolfson and Malchau 2015). PROMs are receiving growing attention because they might give us a clue as to what is different about these dissatisfied patients, enabling surgeons to identify patients who are less likely to benefit from surgery. It has been shown that low self-reported mental health status preoperatively results in poorer subjective outcome (Fisher et al. 2007, Vissers et al. 2012, Khatib et al. 2015), thus suggesting that pre-existing psychological factors have an effect on PROMs.

On the other hand, several studies have also suggested that THA and TKA may even serve to alleviate anxiety and depressive symptoms (Papakostidou et al. 2012, Duivendoorn et al. 2013, da Silva et al. 2014). This beneficial psychological effect is thought to stem from the close relation between chronic pain (as in osteoarthritis) and depressive states (Giesecke et al. 2005, Papakostidou et al. 2012). Finally, a group of patients exhibit “pain catastrophizing”, where intense and excessive concentration on pain sensations preoperatively is associated with a higher risk of persistent pain and an overall worse functional outcome after TKA (Riddle et al. 2010, Vissers et al. 2012, Khatib et al. 2015). Overall, these psychological factors are considered to be modifiable, so preoperative assessment of mental health in THA and TKA candidates may have the potential to improve surgical outcome (Khatib et al. 2015, Rolfson and Malchau 2015).

### Problems of study design

Most studies conducted on surgical outcome after hip and knee arthroplasty in psychiatric patients have been retrospective administrative database studies (Bozic et al. 2012A, B, Stundner et al. 2013, Bozic et al. 2014, Browne et al. 2014, Buller et al. 2015), and have therefore involved several inherent limitations. First of all, most authors have defined psychiatric disease based on diagnostic coding. This is problematic, as patients without these codes—yet treated with psychotropic drugs—may be included in the control group, thus masking the true influence of psychiatric disease on outcomes. Furthermore, there is a risk of misclassification when diagnostic coding provides all the data regarding diagnosis, adverse events, and procedures. Secondly, most of these large database studies only provide in-hospital data. Consequently, potential surgery-related re-admissions and other post-discharge events may not be represented. Thirdly, no or very little information regarding perioperative care is available, which complicates interpretation. This is important, as perioperative care for THA and TKA patients has evolved dramatically in recent years (Husted et al. 2012), while most database studies cover long periods of time dating back to before fast-track surgery was the standard of care.

One recent prospective study with detailed and complete 90-day follow-up was based on a preoperative questionnaire (Jørgensen et al. 2015B) and was cross-referenced to a nationwide database on dispensed prescriptions. Although patients who self-reported a preoperative psychiatric disorder had higher postoperative morbidity, there may be a risk of under-reporting when using questionnaires, although this was compensated for by cross-referencing to dispensed psychotropic drugs. Also, no information on psychiatric diagnoses or indication for psychopharmacological treatment was available, thus preventing conclusions from being reached regarding the role of specific psychiatric diagnoses.

### Future strategies

Recent findings have demonstrated increased LOS, re-admissions, and morbidity in THA and TKA patients with psychiatric disease. These findings are likely to have an important impact on clinical practice because of their scope and severity, so a more thorough and individualized preoperative evaluation of psychiatric patients seems a reasonable strategy. Consequently, some patients might be deemed unfit for surgery or be allocated to an optimized fast-track involving a more vigilant postoperative regime.

More detailed prospective studies in a well-defined fast-track setting are needed to enhance our understanding of the covariates that influence the perioperative course of these patients. Such studies should concentrate on clarifying the complex relationship between psychotropic drugs and psychiatric disease as combined or independent risk factors.

### Discussion

This overview of the literature shows that there is a limited amount of knowledge regarding the interaction between the THA or TKA patient and pre-existing psychiatric disorders or treatments.

Although the studies that have been carried out suggest a complex interaction between psychiatric comorbidity and psychotropic drugs, the question regarding “patient or drug?” remains unanswered. In particular, there is no detailed information regarding severity of the specific psychiatric diagnoses and psychopharmacological treatment. Such information could refine the above-mentioned question from its simple “either/or” form, hopefully resulting in a more balanced research approach.

More detailed studies in the fast-track setting are therefore required to address these questions, especially regarding serious adverse events such as falls and infections. It is crucial that such studies should provide information for strategies for improvement, as previous results suggest that a change in perioperative management is appropriate for this group of high-risk patients (Jørgensen et al. 2015B).

Beyond the immediate postoperative period, the principal aims of arthroplasty are pain relief and improved function. Pre-existing psychological factors also have an effect on these important outcomes, which could influence future patient selection, preoperative education, and timing of surgery in an effort to enhance the proportion of patients who benefit from THA and TKA.

SHG designed the study and drafted the manuscript. CCJ, AF-J, and HK designed the study and revised the manuscript. All the authors read and approved the final manuscript.

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