Appendix 6 (as submitted by the authors)

Mechanisms of Action

Potential mechanisms for the observed associations remain speculative. Soon after their introduction, conventional antipsychotics were suspected of being involved in the development of arrhythmias, cardiac arrest, and sudden death.[7-11] Prolongation of cardiac repolarization and QTc intervals is thought to be responsible and is generally more common with conventional than atypical agents.[12] Anticholinergic properties affecting blood pressure and heart rate, as well as sedation and extrapyramidal symptoms causing potential swallowing problems, are also more common with conventional than atypical agents.[13-17] For these reasons, cardiac (e.g., myocardial infarction and ventricular arrhythmias), cerebrovascular, and infection (e.g., aspiration pneumonia) outcomes may all be potential mediators of any increased risk of death from conventional compared with atypical agents. To date, some[18-20] but not all[8,21,22] epidemiologic studies comparing antipsychotics have found higher risks of ventricular arrhythmia, cardiac arrest and stroke with conventional versus atypical use. Although the present study confirmed the increased risk of non-cancer related mortality with conventional agents in the nursing home population, we were unable to confirm the role of the potential causal mediators, either because of insufficient evidence (i.e., ventricular arrhythmias, cardiac arrest, stroke) or because a positive association was not observed (i.e., pneumonia, heart failure, myocardial infarction).

Antipsychotic use may increase the risk of femur fracture through multiple mechanisms. The well established risk of extrapyramidal symptoms — including parkinsonism and akinesia, rigidity and unsteady gait — associated with the use of conventional antipsychotics is believed to mediate the risk of falls and femur fractures. Although evidence from clinical trials initially indicated a lower propensity of atypical agents to cause gait and movement disorders, there are data suggesting that the risk of developing extrapyramidal symptoms during treatment with atypical antipsychotics is clinically relevant, dose dependent and possibly equal to the risk associated with conventional antipsychotics among older adults with dementia. Atypical APM block D_2 receptors, but they also antagonize serotonergic, muscarinic, histaminergic, and α_1-adrenergic receptors, leading to a possible risk of confusion, delirium, excessive sedation, and orthostatic hypotension, all of which are well established etiologic factors for falls and related femur fractures.[23]

Whether or not antidepressants increase cardiovascular morbidity and mortality is a current topic of debate. While cardiac events have been documented with the use of non-selective serotonin reuptake inhibitors such as tricyclic antidepressants,[24] evidence for a link with selective serotonin reuptake inhibitors is mixed.[25] As is the case for antipsychotics, prolongation of cardiac repolarization and QTc intervals has been postulated as a potential mechanism for increased arrhythmic mortality. Alternative explanations include the effect of depression itself rather than antidepressant use, and imperfect control for pre-existing cardiovascular co-morbidities which are known to be common in patients with depression.[26] Despite control for a wide range of cardiovascular and psychiatric co-morbidities, we observed an increased risk of non-cancer mortality compared with atypical antipsychotics. The effect remained after restricting the population to subjects without a history of depression (HR=1.24, 95% CI 0.98-1.58 in as-treated analyses).

Appendix to: Huybrechts KF, Rothman KJ, Silliman RA, et al. Risk of death and hospital admission for major medical events after initiation of psychotropic medications in older adults admitted to nursing homes. CMAJ 2011. DOI:10.1503/cmaj.101406.

An increased risk for femur fracture has previously been demonstrated for both tricyclic antidepressants and selective serotonin reuptake inhibitor users.[27-31] The explanation may be simply and increased risk of falls resulting from psychomotor impairment and orthostasis, dizziness or altered sleep patterns.[32-34] Another possible explanation is the effect of antidepressants on bone physiology through inhibition of the 5-hydroxytryptamine transporter system. Stronger inhibition of the 5-hydroxytryptamine transporter could cause a greater disruption of the balance between osteoblasts and osteoclasts and hence have a greater detrimental effect on bone micro-architecture.[35]

Benzodiazepines have been implicated as a cause of numerous adverse events, most importantly a worsening of memory loss, falls and hip fractures, even with shorter half-life agents, modest dosages, medium durations of use, and the newer sedative hypnotics.[36] We observed a fracture risk at least as high as that of users of atypical antipsychotics. Since atypical antipsychotics users have been shown to be at increased risk of hip fracture compared with non-users,[23] our findings indicate an increased fracture risk for benzodiazepine users, with the risk being the same order of magnitude as that of atypical antipsychotics users.

We are unaware of previous research documenting an increased risk of heart failure with benzodiazepine use. The effect remained, and was in fact stronger, when restricting the population to subjects without a documented history of heart failure. Further research is needed to determine whether this might be a chance finding.

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