Is antipsychotic sensitivity in Alzheimer’s disease secondary to abnormal blood–brain barrier integrity?

This scientific commentary refers to ‘Therapeutic window of dopamine D2/3 receptor occupancy to treat psychosis in Alzheimer’s disease’, by Reeves et al. (doi:10.1093/brain/aww359).

Elderly persons are more sensitive to the adverse effects of antipsychotic drugs. Thus, the need to minimize these adverse effects when treating aggression, agitation and psychosis in patients with Alzheimer’s disease has become paramount. However, scant information on pharmacokinetics (relationship between dose, systemic drug concentrations, and time) and pharmacodynamics (relationship between systemic drug concentration and the effect of the drug over time) exists to inform minimally effective antipsychotic dosing guidelines for Alzheimer’s disease. In developing such guidelines for treating behavioural symptoms, much can be drawn from psychiatry’s efforts to elucidate the mechanism of action and therapeutic window of antipsychotic drugs. In this issue of Brain, Reeves et al. build upon these efforts by using PET to determine how blood concentrations of the antipsychotic amisulpride relate to occupancy of brain dopamine D2-type (D2) receptors, and in turn, therapeutic and adverse effects in elderly patients with Alzheimer’s disease (Reeves et al., 2017).

In the early 1950s chlorpromazine, with its ability to produce a ‘calm quietude’, was successfully used in the treatment of psychosis. It was not until the late 1970s that the clinical efficacy of doses of antipsychotics was found to correlate with their ability to inhibit dopamine D2 receptors in striatal membranes in vitro (Seeman et al., 1975). With the development of radio-labelled ligands that could bind to D2 receptors, it became possible to quantify the availability of D2 receptors in the living human brain using PET. Soon after, it became apparent that antipsychotics did bind to striatal D2 receptors in patients with schizophrenia in vivo, blocking the binding of D2-prefering radioligands (Farde et al., 1988). Translating the earlier ex vivo work, several PET studies suggested a ‘therapeutic window’ of striatal D2 receptor occupancy by antipsychotics; 65–80% occupancy was associated with a positive clinical response, while occupancies above 80% were likely to induce unwanted extrapyramidal and endocrinological side-effects (Howes and Kapur, 2009). Notably, elderly patients with schizophrenia (age ≥ 50) were more sensitive to extrapyramidal side effects of antipsychotic drugs, showing side effects at lower drug occupancies (<80%) compared to younger patients (Graff-Guerrero et al., 2015; Iwata et al., 2016; Nakajima et al., 2016).

Given that striatal D2 receptor expression and dopamine synthesis decrease with age, it was suggested that this may be due in part to pharmacodynamic changes with ageing. Using PET, efforts have been made to establish minimally effective dose-D2 receptor occupancies for elderly patients with schizophrenia, which may be closer to 50% (Graff-Guerrero et al., 2015) with an upper threshold of 66% for side-effects (Iwata et al., 2016).

However, it is unknown how D2 receptor occupancy by antipsychotics relates to clinical response in elderly patients with Alzheimer’s disease. Reeves et al. are the first to attempt to elucidate this information in Alzheimer’s disease with psychosis, and provide important empirical data linking psychosis (i.e. hallucinations and delusions) with an aberrant dopaminergic state in Alzheimer’s disease. The link between psychosis and dopamine has been informed by two converging lines of evidence that support the dopamine hypothesis of schizophrenia. The first was the observation that d-amphetamine, and related compounds that enhance dopaminergic neurotransmission, elicit a psychotic state (Abi-Dargham et al., 2009). The second was the discovery that antipsychotics cause increased central monoamine turnover, and that all antipsychotics bind to D2 receptors (Carlsson and Lindqvist, 1963). Soon thereafter, it was shown that antipsychotics antagonize amphetamine-induced psychotic states, thereby linking aberrant dopamine transmission with psychotic symptoms and antipsychotic action. While the original idea of dysregulated striatal dopamine transmission in schizophrenia has been confirmed by neuroimaging studies, which show increased dopamine synthesis, increased release of dopamine in response to a challenge, and a higher level of synaptic dopamine (Howes and Kapur, 2009), the mechanism of psychosis in Alzheimer’s disease is only supported by the association between psychotic symptoms and antipsychotic action.

Using population-based pharmacokinetic models in conjunction with 18F-fallypride PET, Reeves et al. characterize the relationship between blood concentrations of the antipsychotic amisulpride and central D2 receptor occupancy. Notably, low average blood concentrations of amisulpride (71 ± 30 ng/ml) were associated with high central D2 receptor occupancies in the striatum (caudate ~65%; putamen ~52%) and thalamus (~67%). Importantly, a blood
concentration threshold of 60 ng/ml was associated with extrapyramidal symptoms, and similarly high D₂ receptor occupancies (caudate ~61%; putamen ~49%). The threshold for clinical response was noted at 20 ng/ml, with low D₂ receptor occupancies (~43% caudate; ~23% putamen). The relationship between antipsychotic blood concentration and central D₂ receptor occupancy has been used to predict the therapeutic dose range of novel antipsychotics and to generate recommendations for the dosage of antipsychotics (Nakajima et al., 2016). However, the routine measurement of D₂ receptor occupancy with PET for clinical purposes is not feasible due to poor availability and high cost. Previous studies, supported by antipsychotic D₂ receptor occupancy PET results, have generated bedside occupancy prediction models (Nakajima et al., 2016). The data presented by Reeves et al. could generate an occupancy prediction model specifically for Alzheimer’s disease, requiring only widely available blood quantification of antipsychotics to be implemented in clinical practice. The generation of bedside occupancy prediction models to individualize antipsychotic dosing is also relevant for the treatment of Alzheimer’s disease dementia due to the strong inverse association between cognition and antipsychotic dose (Rajji et al., 2017). The framework provided by Reeves et al. could be employed to test this inverse association, specifically in Alzheimer’s disease, and to minimize the potential antipsychotic burden on cognition.

Reeves et al. have established for the first time that there is a ‘therapeutic window’ of central D₂ receptor occupancy by antipsychotics for treating psychosis in persons with Alzheimer’s disease. This concept is similar to that observed in patients with schizophrenia. However, in Alzheimer’s disease higher than anticipated central D₂ receptor occupancies were observed for given blood concentrations of amisulpride. While older patients with schizophrenia demonstrate side effects at lower D₂ receptor occupancies than younger patients, the relationship between drug concentrations and occupancy remains similar. Thus, Reeves et al. suggest that, unlike what has been proposed in schizophrenia, the increased sensitivity to antipsychotics in Alzheimer’s disease may be primarily due to pathological pharmacokinetic changes—such as reduced blood–brain barrier integrity—rather than pharmacodynamic ones. While

Figure 1 Heuristic model to illustrate that antipsychotic concentrations in blood and brain are similar in younger and older patients with schizophrenia. The high sensitivity to antipsychotics in older patients with schizophrenia seems to be associated with pharmacodynamic changes associated with ageing (i.e. decreased density of D₂ receptors and decreased dopamine synthesis). The current report by Reeves et al. suggests that in Alzheimer’s disease, there is an additional disruption of the blood–brain barrier transporter that significantly contributes to antipsychotic sensitivity (bottom), in addition to changes associated with ageing. Note that the model shows similar blood antipsychotic concentration in the three scenarios. The occupancies are only to illustrate the effect of changes in pharmacodynamics and pharmacokinetics.
future work is required to uncover the mechanism(s) by which patients with Alzheimer’s disease are more sensitive to antipsychotics, the findings by Reeves et al. mark an important first step, within a long history of research, aimed at guiding the rational dosing of antipsychotics. These mechanisms may differ across disorders (e.g. schizophrenia versus Alzheimer’s disease) and be influenced by physiological changes associated with ageing.

Fernando Caravaggio1,2 and Ariel Graff-Guerrero3,4

1Multimodal Imaging Group—Research Imaging Centre, Centre for Addiction and Mental Health, Toronto, Canada
2Department of Psychiatry, University of Toronto, Toronto, Canada
3Institute of Medical Science, Faculty of Medicine, University of Toronto, Canada
4Geriatric Mental Health Division, Centre for Addiction and Mental Health, Toronto, Canada

Correspondence to: Dr Ariel Graff-Guerrero M.D., Ph.D.
E-mail: ariel.graff@camh.ca

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