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Invited Letter Rejoinder

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Antipsychotic drugs: from 'major tranquilizers' to Neuroscience-based-Nomenclature

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We highly appreciate Professor Moncrieff's work and we find it very important that there are critical minds who challenge the 'mainstream', which in the history of medicine has often been proven wrong. We would like to be counted among these critical minds. Nevertheless, the public debate about psychotropic agents is often ideological rather than evidence-based. Therefore, although Professor Moncrieff did not explicitly write that antipsychotics are just unspecific sedatives, such arguments are often used making our systematic review important (Siafis et al., 2019).

Antipsychotic drugs

The introduction of antipsychotic agents in 1950s and their apparent efficacy was shortly followed by a tremendous reduction of institutionalized patients with schizophrenia. To deinstitutionalize patients was also based on general political decisions, but it is doubtable whether it would have been possible to the same extent without the availability of effective medication. Historically, these agents were called major tranquilizers or neuroleptics, but in the late 1960s, even before the establishment of dopamine theory of schizophrenia, they started to be described as antipsychotics, because they could improve fundamental symptoms of schizophrenia, i.e. thought disorder, blunted affect and withdrawal as well as secondary symptoms of hallucinations and delusions (Davis & Kline, 1969). In addition to their established efficacy in treating acute exacerbations of schizophrenia (Huhn et al., 2019) and preventing relapses (Leucht et al., 2012), there is also more recent evidence on their efficacy in patients with predominant negative symptoms; at least for amisulpride (lower doses 50–300 mg/day) and cariprazine (Krause et al., 2018).

All current antipsychotics target $D_{2/3}$ receptors, yet each has a distinct receptor-binding profile (Fig. 1) and subsequently, a different side-effect profile (Huhn et al., 2019). Antipsychotics have per definition 'psychoactive' effects, including negative subjective experiences (Moncrieff, Cohen, & Mason, 2009) that could be associated with the antagonism of dopamine receptors or other receptors. Due to this general 'dampening' and the multiple side-effects, antipsychotics are indeed among 'the bitterest pills' (Moncrieff, 2013). However, these effects are well known and unfortunately, there is no other treatment which is effective in monotherapy. In general, there is a therapeutic window of $D_{2/3}$ antagonism, since occupancy on $D_{2/3}$ receptors is related to both clinical response and negative subjective well-being (Kaar, Natesan, McCutcheon, & Howes, 2019). Therefore, dosing needs to be carefully adjusted at an individual level in order to balance benefits and harms. Moreover, the multiple antipsychotics available have different side-effects, and some are generally more benign (Huhn et al., 2019). Nevertheless, it is clear that there is an enormous need for the development of better tolerable and more efficacious drugs to treat schizophrenia.

The neurobiology of schizophrenia is not well understood, but dopaminergic and excitatory-inhibitory dysfunctions are the current leading neurobiochemical hypotheses (Howes, McCutcheon, & Stone, 2015). Psychological factors, such as early childhood trauma, urban living, ethnic minority status, and substance abuse have also been clearly associated with the development of schizophrenia (McCutcheon, Reis Marques, & Howes, 2019). Therefore, it cannot be stated with certainty, whether the dopaminergic dysfunction is an epiphenomenon and how the mechanism of action of antipsychotics relates to the pathophysiology of schizophrenia or other mental disorders, and antipsychotics might target downstream pathways rather the main underlying dopaminergic dysfunction (Jauhar et al., 2019). In addition, the multi-receptor effects of antipsychotics and the overlap among diagnostic entities could explain their broader effects e.g. their antidepressant and anti-manic effects. In order to bridge these uncertainties and decrease confusion, the pharmacology-driven nomenclature NbN (Neuroscience-based-Nomenclature) has been proposed (Zohar et al., 2015). It is quite gross and imperfect, but certainly better than previous distinctions such as 'minor *v.* major

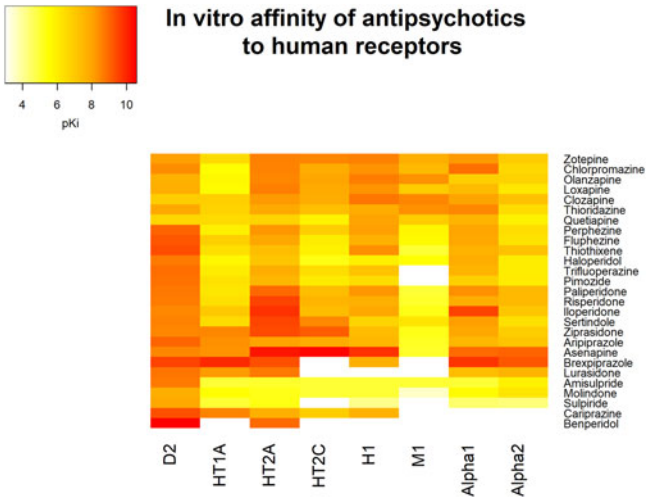

Fig. 1. In vitro binding profile of antipsychotic drugs. The inhibitory constant [Ki (nM)] to human receptors was extracted from PDSP (Besnard et al., 2012), and IUPHAR/BPS (Armstrong et al., 2019). When more than one values were reported for the same receptor, the median was used. The pKi was calculated. The higher the value of pKi, the higher the affinity of the antipsychotic to the receptor. Not available pKi values are demonstrated with white color. D2: dopamine receptor D_2, HT1A, HT2A, HT2C: serotonin receptors 5-HT_{1A}, 5-HT_{2A}, 5-HT_{2C}, H1: histamine receptor H_1, M1: muscarinic M_1 acetylcholine receptor, Alpha1, Alpha2: α_1 and α_2 adrenoceptors.

tranquilizers', 'low-potency *v.* high-potency' or 'atypical *v.* typical', a term which has been much abused by pharmaceutical industry marketing.

Antipsychotic drugs and 'sedatives'

In our introduction, antipsychotic drugs were not claimed to be merely active placebos or identical to other sedatives, rather the 'failure to establish clear differences with non-specific drugs' (Moncrieff & Cohen, 2005) was emphasized. We believe that our review further elucidated this discussion. We found sufficient evidence that antipsychotic drugs were superior to phenobarbital for acute schizophrenia, yet evidence on the comparison with benzodiazepines was inconclusive because it was based on a single small trial (80 participants including the inert placebo arm) with large response rates in all arms (65% in inert placebo and benzodiazepines, 75% in chlorpromazine), small doses of chlorpromazine (about 150 mg/day), and the trial being sponsored by the company manufacturing the benzodiazepines (Merlis, Turner, & Krumholz, 1962; Siafis et al., 2019). We also want to add that in a small trial (not meeting the inclusion criteria of our review because it was conducted in stable patients) in 53 patients with schizophrenia, diazepam was comparable to fluphenazine and superior to placebo in preventing progression to a full relapse when used for early signs of exacerbation after the abrupt discontinuation of antipsychotics (Carpenter, Buchanan, Kirkpatrick, & Breier, 1999). Benzodiazepines have also been found efficacious in very short-term sedation of acutely agitated patients with schizophrenia (Dold et al., 2012). Therefore, future trials are warranted for benzodiazepines, yet clinical importance is questioned because of their abuse potential and increased mortality (Tiihonen, Suokas, Suvisaari, Haukka, & Korhonen, 2012).

Summary

In summary, antipsychotic drugs should not be deducted to merely 'sedatives' and they are the only effective monotherapy for schizophrenia, though there are still questions about their exact mechanism of action, longer-term use, and treatment-resistance. Due to their multiple adverse effects, better tolerable and more specific treatments need to be developed. Clinical practice and research could be facilitated by using pharmacology-driven classifications of psychotropic drugs.

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