Antipsychotic action and symptom specificity - down the bioinformatic rabbit hole [Letter to editor]

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Antipsychotic action and symptom specificity - down the bioinformatic rabbit hole.

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Bioinformatics in psychiatry is a young concept; the ten years from 2011 saw a ten-fold rise in related publications. This reflected the rapid expansion of databases containing large amounts of clinical, genetic and other biological information from large numbers of individuals, along with the relative ease with which they can be interrogated. No doubt this can and will contribute enormously to our understanding of psychiatric disorders and their treatment. However, studies need to be securely grounded in clinical evidence and biological rationality. A recent publication in this journal has, I believe, not clearly demonstrated how it has adhered to this essential tenet.

Zhuo et al (2025) report a computational bioinformatic analysis aiming to identify molecular mechanisms relating to, and differentiating, antipsychotic drug effects at positive and negative symptoms. In principle this is a potentially very

valuable aim, since the efficacy of these drugs, particularly on negative, cognitive and depressive symptoms of schizophrenia, are very limited.

The explicit assumption of this study is that haloperidol, sulpiride and KarXT (the recently US-approved xanomeline-trospium combination) are distinguishable in their relative effects on positive and negative symptoms of schizophrenia. The clinical premises underlying this approach appear to have little, if any, supporting evidence. This includes the suggestion that sulpiride (at low dose) has a particular efficacy on negative symptoms. The references provided to support this are a small 1987 study of high vs low dose sulpiride, and a Cochrane review superseded by one which reports that "there were no clear differences (from placebo for) either positive or negative symptoms" (Wang and Simpson, 2014). There is no comparative data to indicate sulpiride is more effective than any other antipsychotic in relieving negative symptoms, and network meta-analyses show it to have overall efficacy very similar to haloperidol (Huhn et al 2019)

A further concern is the absence of evidence differentiating KarXT from second generation antipsychotic drugs in any aspect of its efficacy (Wright et al 2024). Thus it does not appear to be distinguished by relieving both positive symptoms better than sulpiride and negative symptoms better than haloperidol, as suggested by Zhuo et al (2025). It is notable that each of the recently introduced antipsychotics has been suggested to have a particular efficacy in relieving negative symptoms, but this rarely proves true in clinical practice.

Notwithstanding these limitations, the authors have undertaken an elaborate bioinformatic analysis involving the identification of biological targets associated with positive and negative symptoms. This analysis is not completely transparent. What exactly is meant by "target" may differ between the interrogated databases depending, for example, on how the association between gene and drug is identified. Taking BDNF, identified as the first sulpiride target: a search in GeneCards (one of several databases used by the authors) for genes associated with sulpiride ranks BDNF in position 98 (https://www.genecards.org accessed 3rd Dec 2025). Its rationale for listing appears to be from the co-occurrence of the MESH terms "BDNF" and "sulpiride" in two publications: one showing no effect of amisulpride on plasma BDNF (unlike olanzapine; sulpiride was not studied), the other showing sulpiride can block, likely via D2 inhibition, hypoxia-induced BDNF release from a neuronal cell line. This can hardly constitute evidence for BDNF as a valid pharmacological target for sulpiride's (limited) efficacy. It is sobering to think that the publication of Zhuo et al (2025), and even this letter, may in the future be taken as further bioinformatic evidence for an association between sulpiride and BDNF!

This example relates to just one of several hundred targets identified by the authors and may not necessarily extrapolate to all their findings and conclusions. I fully acknowledge that other approaches were used to come to their conclusions, so there may be other and better evidence justifying BDNF and other gene products as specific antipsychotic drug targets. Perhaps the sheer power of bioinformatics can let us overlook what may be argued are only minor weaknesses. Nevertheless it would be valuable to have some transparency, and rationality, in the identification and choice of mechanistic targets provided by empirical evidence. Future work should bear in mind the old computer science acronym: GIGO.

Huhn M, Nikolakopoulou A, Schneider-Thoma J et al. (2019) Comparative efficacy and tolerability of 32 oral antipsychotics for the acute treatment of adults with multi-episode schizophrenia: a systematic review and network meta-analysis. *Lancet* 394(10202):939-951.

Wang J, Sampson S. (2014) Sulpiride versus placebo for schizophrenia. *Cochrane Database Syst Rev*. 2014(4):CD007811.

Wright AC, McKenna A, Tice JA, Rind DM, Agboola F. (2024) A network meta-analysis of KarXT and commonly used pharmacological interventions for schizophrenia. *Schizophr Res*. 274:212-219.

Zhuo C, Li C, Ma X, Li R, Chen X, Li Y, Zhang Q, Yang L, Tian H, Wang L. (2025) KarXT combines the partial benefits of haloperidol for positive symptoms and sulpiride for negative symptoms: Evidence from computational biology. *J Psychopharmacol*. 39(11):1307-1319.