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Strategic and tactic use of antipsychotic medications in schizophrenia: a perspective on current prescription practice

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Abstract

Antipsychotic medications (APs) are pivotal in treating schizophrenia, alleviating symptoms like delusions, hallucinations, and disorganized behavior. APs can induce extrapyramidal symptoms and sedation, complicating chronic use but aiding in acute management. AP-induced metabolic syndrome, a primary factor in reduced life expectancy, is not a major concern during short-term treatment. Studies on APs efficacy yield mixed results, leading to trial-and-error prescribing practices. Meta-analyses indicate clozapine, amisulpride, olanzapine, and risperidone as effective in acute settings, with olanzapine and haloperidol beneficial for SZ-related agitation. Empirical observations suggest higher potency APs, like olanzapine and haloperidol, are more effective in acute psychosis, with zuclopenthixol also advantageous for its sedative properties. Cariprazine, lurasidone, low-dose amisulpride, brexpiprazole and aripiprazole showed a favorable side effects profile and a potential benefit on negative symptoms. My proposal in this perspective paper is to consider schizophrenia as a relapsing–remitting disorder, requiring a different pharmacological approach in the acute and maintenance phases. In the initial phase a high-dose, high-potency and fast-titrating AP should be used, for rapid symptoms' control (i.e. haloperidol, olanzapine, risperidone, high-dose amisulpride, zuchlopenthixol), defined as a *tactic AP*. Once the acute phase resolved, patients should be gradually switched towards a medication with fewer side effects (i.e. metabolic syndrome, extrapyramidal symptoms, hyperprolactinemia) and a potential efficacy on negative symptoms and personal functioning (i.e. cariprazine, low-dose amisulpride, lurasidone, aripiprazole, brexpiprazole), to be continued in the long term, defined as a *strategic AP*. This approach aligns with empirical observations and aims to refine schizophrenia care through phase-specific APs use, necessitating further studies to validate its efficacy.

Keywords Treatment personalization, Antipsychotics, Acute psychosis, Side effects management, Psychomotor agitation

Antipsychotic medications (APs) are the cornerstone in the treatment of schizophrenia; their activity on dopamine and serotonin receptors, located at multiple sites in the mesolimbic and meso-cortical pathways and on glutamatergic pyramidal neurons accounts for the antipsychotic effect sensu-stricto (i.e. on delusions, hallucinations, thought process and behavioural disorganization) [1, 2]. The binding to dopamine receptors could also provoke extrapyramidal symptoms (EPS), and the binding to muscarinic, H1 histaminergic and alfa-1 adrenergic receptors is responsible for sedation [3]. While in the context of a chronic treatment sedation and motor slowing constitute an unbearable burden, in the acute setting they aid in controlling psychomotor agitation. Besides, a main cause for the reduced life expectancy in SZ is metabolic syndrome, which does not represent a major concern in the early acute setting, since a few days of AP treatment alone don't significantly impact this outcome in the long-term.

Studies comparing the efficacy of APs produced mixed results; as a consequence, the AP choice is a matter of trials and errors, depending on prescriber's beliefs and other contingencies, and the leading guidelines (National institute for the excellence of care, NICE [4]; World federation of Societies of biological psychiatry: guidelines for biological treatment of schizophrenia, WFSBP [5]) only recommend to choose an AP with limited side effects. The other key point of reference in prescribing APs, the Maudsley guidelines, recommends using monotherapies, reserving the combination of two medications for treatment resistant schizophrenia [6].

Meta-analyses [7, 8] indicate clozapine, amisulpride, olanzapine and risperidone as the most effective choice in the acute setting. Comparative studies on efficacy in the maintenance phase, on the other hand, are lacking [9].

Olanzapine and haloperidol resulted the best option for schizophrenia-related psychomotor agitation, as an alternative to other effective choices, such as ziprasidone and, to a lesser extent, aripiprazole [10–12].

Beyond the results of controlled studies, a common-sense experience is that medications like olanzapine, haloperidol, high-dose amisulpride, paliperidone and risperidone are more incisive on the acute psychosis, in line with their high potency on D2 and/or 5HT2A receptors; moreover, medications as zuclopenthixol and fluphenazine present a strong sedative effect, which could be beneficial for severely agitated patients [13]. The advantages of these medications are likely to be limited to the first few days of hospitalization, while the studies on the acute setting cited above evaluated efficacy on a 6–8 weeks' time span. This is likely to explain why for some of these medications the difference in efficacy compared to others had a small effect size, or no differences emerged at all in previously cited meta-analyses.

Lacking strong evidence on the first days of treatment, theoretical knowledge of a higher antipsychotic and sedative potency of certain APs should guide in the AP selection in the initial phase of treatment.

Schizophrenia is classically decomposed in the three dimensions of positive, negative and cognitive symptoms [14]. While the efficacy of APs on the acute positive symptoms phase is clear, evidences on their efficacy in the negative dimension is lesser: only cariprazine [15] and low-dose amisulpride [16, 17] showed a positive impact. Moreover, a metanalysis suggested that aripiprazole might be effective as add-on medication to

reduce negative symptoms [18]. Quite the opposite, especially first-generation APs have the potential to induce secondary negative symptoms [19].

The aim of this perspective paper is to propose a novel paradigm in the use of APs, in order to entirely harness their potential. While not a systematic review of the literature, the paper is grounded on the meta-analytical, clinical and pre-clinical evidence cited above, and on some common-sense, empirical knowledge of the "real-world" psychiatrist. The ultimate aim is to prompt studies assessing the validity of the proposed new way of prescribing APs.

Given that APs primarily impact positive, disorganized and aggressive symptoms, this paper mainly focuses on these, while also emphasizing the importance of preventing secondary negative symptoms induced by APs.

The position expressed below do not consider treatment resistant schizophrenia [20, 21]. Given the therapeutic superiority of clozapine and the overall favourable balance between efficacy and side effects, clozapine and clozapine augmentation strategies have to be considered in the first place [20, 21]. The use of alternative primary APs doesn't seem a valid choice in the acute and in the maintenance phase of treatment resistant schizophrenia.

First, schizophrenia should be regarded as a relapsing–remitting disorder, in which acute psychotic episodes are followed by remission. Different priorities correspond to the two phases, and the meaning of therapeutic and side effect change from on to the other, as well. Also, the determinants of safety are not the same, being in the former often linked to behavioral events, and in the latter on extrapyramidal side effects, sedation, metabolic syndrome and hyperprolactinemia.

In the acute setting, patients benefit from a high antipsychotic potency, to shorten the duration of untreated psychosis (DUP) and to deal with psychotic anxiety; moreover, sedative and anti-dopaminergic effect (cutting the motivational drive) are useful to manage psychomotor agitation. High potency should be deployed by choosing a high potency AP at a high in-label dose; moreover, a fast up-titration should be sought and AP for whom it is possible should be privileged. A sedating AP should be chosen when necessary to deal with psychomotor agitation, anxiety and insomnia, not relying only on benzodiazepines to this end, but on a multimodal sedation based also on anticholinergic, antihistaminic and antiadrenergic effects.

Based on the abovementioned meta-analyses [7, 8] and on real-world knowledge, an AP among olanzapine, haloperidol, zuchlopenthixol, risperidone, paliperidone and high-dose amisulpride should be preferred for the acute treatment of schizophrenia.

To rely on 3rd generation APs in the acute phase could be a mistake, due to low potency and slow titration; however, this aspect also depends on the history of disease, being a first episode of psychosis more likely to respond to low doses of low-potency drugs, especially if the DUP was short. In selected cases, it could therefore be appropriate to rely on this kind of medications since the beginning, in the presence of a lower severity of disease and of other positive prognostic factors (e.g. good cognitive and social functioning, male sex, early response to the medication, no comorbidities) [22].

Once the acute psychotic episode resolved, the focus of the treatment is to keep the remission, to treat negative symptoms, to improve personal, interpersonal and working functioning, and to limit side effects; on the contrary, a high antipsychotic potency is probably no more useful.

Even if the APs cited above are more effective in the acute phase of schizophrenia, there isno evidence that it is true also for the maintenance phase [9], and the potential higher efficacy is probably outshadowed by side effects. Therefore, a monotherapy with a 2nd generation (SGA) or 3rd generation AP (TGA), having limited side effects, should be chosen. An intermediate dosage should be adopted at the end of the acute psychotic episode, and the longer the remission persists, the more the AP should be down titrated, considering that the longer the disease-free duration the lesser the likelihood of a novel acute psychotic episode [6, 23].

In the maintenance phase other common mistakes are to never change the AP chosen during an acute episode, and/or to add another AP to improve residual symptoms, adopting an augmentation instead of a switching strategy.

The present proposal is to adopt a specific AP in the acute and in maintenance treatment of SZ, in order to have a treatment fitting the need of each phase, and only briefly overlapping one with the other. A high potency AP (e.g. haloperidol, zuchlopentixol, olanzapine, high-dose amisulpride, risperidone, paliperidone), suiting best the acute phase (*tactic AP*), should be started at high dose; when a substantial response to this medication is observed, normally after 7 to 10 days, a gradual switch towards an AP appropriate for the maintenance phase should be started (*strategic AP*), including lurasidone, aripiprazole, brexpiprazole, cariprazine or low-medium dose amisulpride. It is possible that a further dose reduction is feasible, but keeping a dose superior to 200 chlorpromazine equivalents and paying a particular attention in younger patients, in order to avoid relapses [23–25]. Moreover, dose reduction could lead to a better cognitive and social functioning [26], especially in the long-term [27].

An advantage of the strategic AP is its pro-cognitive effect, with a low-to-medium effect size; however, even if a benefit was found with TGA and lurasidone [28, 29], the evaluation of the pro-cognitive effect of the APs should be cautious, as indicated by a recent meta-analysis [30].

Even if not all the studies demonstrated a significant better metabolic safety of TGA and lurasidone compared to other second-generation APs [31], synthesis of evidence suggests a clear advantage with low-to-moderate effect size for these medications [32].

Last, to further improve negative symptoms management, antidepressant should be prescribed in the maintenance phase [33, 34], as supported by meta-analytic evidence [35, 36] and review of clinical trials [37] that indicate a moderate effect of this kind of prescription.

While the long-acting injectable formulation is considered a better therapeutic strategy in schizophrenia [38], it limits the choice to only one of the possible strategic AP, aripiprazole; accordingly, this choice should be made only if necessary to guarantee the adherence to treatment, and regular blood collections could be considered as an alternative approach.

In conclusion, the present proposal aims to better utilization of each AP, considering its peculiar pharmacological profile and based on the conceptualization of schizophrenia as a relapsing–remitting disorder. Accordingly, APs should be used differently in the acute phase and in remission, concerning active principles and dosages. Further studies, based on novel data should be performed to test our hypothesis, and its ability to improve the quality of care in schizophrenia.

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