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There are no "side" effects, just "core" effects of antipsychotic pharmacotherapy

In this issue of Acta Psychiatrica Scandinavica, Stahl et al. bring our attention to the most common side effects of antipsychotic drugs providing practical yet scholarly guidance toward their optimal management.[1]

Schizophrenia is a chronic psychiatric disorder with a heterogeneous combination of symptoms. Characteristic, but by no means exclusive, symptoms of schizophrenia include "positive," "negative," and "cognitive" categories. Each category is expressed as a broad set of dysfunctions which manifestations may fluctuate during the lifetime. Therefore, optimal management of schizophrenia should aim to address multiple domains and degrees of severity, ideally minimizing the "side effects" of the antipsychotic drugs, medications that represent the cornerstone treatment of schizophrenia.[2]

As noted by Stahl et al.,[1] the management of antipsychotic-induced adverse events (AEs) often proves to be a daunting task, reflecting the complexity of illness. In their report, Stahl et al. provide a narrative synthesis based on the most clinically relevant randomized clinical trials (RCTs) and systematic reviews stressing out the need to prescribe the antipsychotic drugs based on their effect and efficacy profiles. In other words, the prescribing clinician is solicited to account for both RCT and real-world based evidence. A comprehensive overview of the most common motor, psychological, and metabolic "side" effects induced by the broadly adopted antipsychotic drugs is presented alongside rational guidance about the clinical detection and management of the most common adverse outcomes.

Overall, as remarked by Stahl et al., not even the most recently introduced compounds are entirely void of potential AEs, including serious or potentially life-threatening ones.[3] The overall recommendations drawn by Stahl et al.[1] are in line with both qualitative[4] and quantitative evidence about the safety and tolerability of short- (emergency use) and long-acting antipsychotics in the acute treatment of adults with multi-episode,[5] as well as first-episode[6] schizophrenia, especially concerning the cardio-metabolic impact of the atypical antipsychotics.[7] Prescription of antipsychotics for conditions other than schizophrenia is on the increase, often—in the long-term—resulting in varying safety and tolerability problems, which may affect patients of all ages.[8] Also, the antipsychotic drugs are just as heterogenous as are the clinical manifestations of schizophrenia.

As customary, the report by Stahl et al. is a high-quality piece of work, not just a primer for the younger psychiatrists, I should say. Personally, I would like to further stress the importance of focusing on the adverse effects induced by antipsychotic drugs besides efficacy considerations. We must not consider the management of the antipsychotic AEs as a "second-tier" goal, or something we should postpone too much (ideally, we should account for that events early in the treatment stages, better before the treatment begins).

As extensively reviewed by Moncrieff in the year 2013, the concept of the "antipsychotic" drug is a relatively novel one, at least in the way we consider it nowadays.[9] Professor Hans Steck of Lusanne and the German psychiatrist Hans Joachim Haase independently provided the first unambiguous reports of the phenothiazine drug chlorpromazine's effects on the neurological motor symptoms—what it is now generally referred to as extra-pyramidal symptoms—in the year 1954. They also described the drug-induced inner tension and motor agitation known as akathisia.[9] The French Drs. Jeanne Delay and Pierre Deniker already noted the sedative effects and apathy induced by the first antipsychotic drug, chlorpromazine, in 1956. However, they considered that events as incidental than primary effects induced by the drugs.[9] Back in 1958, the Belgian researcher Dr. Paul Janssen, who provided a crucial role in the development and marketing of the butyrophenone haloperidol, would not even consider a drug as a medication potentially active in the management of psychosis if it would not induce Parkinsonism or other "core" effects, considered as "inseparable" part of the (therapeutic) effect of the drug itself.[9]

The modern paradigm about the use of the so-called antipsychotic drugs changed a lot over the past decades. Ideally, the modern prescribing clinician should carefully consider several issues in selecting the "optimal" antipsychotic medication for people with schizophrenia, as critically appraised elsewhere.[10] The first dilemma is about whether to treat schizophrenia (with an antipsychotic drug, at a given time in the life of the suffering one). In a recent meta-analytic review exploring the association between long-term mortality

and antipsychotic use in people with schizophrenia, a *lower* rate of all-cause mortality was documented among patients with any antipsychotic exposure compared with people with schizophrenia who did not receive antipsychotics (pooled risk ratio = 0.57, $p < .001$, after adjusting for several confounding factors).[11] Thus, although chronic exposure to antipsychotics can inflate the risk for metabolic events, the available evidence suggests a favorable risk-to-benefit ratio.[12] However, it largely depends on what we, as clinicians,[3] and the patient as the recipient, consider a clinically relevant AE, a paradigm which changed over the past decades.

A second dilemma relates to adherence. Treatment adherence is crucial when it comes to life-lasting conditions, often requiring lifetime care. Approximately 50% of people with schizophrenia present with poor adherence to the prescribed medications, and upwards of 75% become non-adherent within two years of hospital discharge.[13] Either oral or long-acting antipsychotics leading to major AEs mine the overall adherence of people with schizophrenia, which is a critical issue considering both the associated psychosocial burden, the lower propensity to engage in any further pharmacological treatment after withdrawal, or the risk to develop resistance toward subsequent trials as the neuroprogression of schizophrenia worsens.[2]

Sir William Osler once said, "The good physician treats the disease; the great physician treats the patient who has the disease. The great physician understands the patient and the context of that patient' illness.".[14] While we, the psychiatrists, certainly have something to learn essentially by merging high-quality, evidence-based medicine with real-world clinical practice, it is evident that we also have something to teach aiming at promoting the quality of life of the suffering patients. This duty indeed lies with our residency programs and the need to take a fresh and thorough look at the controversy surrounding the hierarchical treatment approach to schizophrenia, historically promoting anti-delusional and sedative goals over tolerability and safety.[15] Finally, there are no "side" effects, just "core" effects to bear in mind, in line with a patient—rather than a disease or symptom-based approach. A "critical" reading of even a masterpiece as the one provided by Stahl et al.[1] should not leave aside such insight.

DECLARATION OF INTEREST

None declared.

Michele Fornaro

Section of Psychiatry - Department of Neuroscience, Reproductive Sciences, and Dentistry, University School of Medicine Federico II, Naples, Italy
Email: Dott.Fornaro@gmail.com

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