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Antipsychotics and Attenuated Psychosis Syndrome: Transdiagnostic assessment and discontinuation strategies

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Dear editor,

In emerging psychosis stages, affective dysregulation may predate attenuated psychotic symptoms as feeling mildly paranoid, as illustrated in the clinical case of Sarah, detailed in Fig. 1. Sarah's presentation is consistent with an increased vulnerability for developing psychosis.

This vulnerability can be conceptualised according to the Clinical High Risk for Psychosis (CHR-P) criteria, which are defined with psychometric instruments such as the Comprehensive Assessment of At-Risk Mental State (CAARMS) (Fusar-Poli et al., 2020), or the Attenuated Psychosis Syndrome, according to the DSM-5 (DSM5-APS) (Salazar de Pablo et al., 2019). Meeting CHR-P/DSM5-APS criteria is associated with about a 20% probability of developing a first episode of psychosis over time at 2 years, 29% at 4 years and 35% at 10 years (Salazar de Pablo et al., 2021b). Being detected as CHR-P/DSM-5-APS facilitates for young people to be offered a package of preventive care with the potential to improve their outcomes and quality of life (Fusar-Poli et al., 2020; Salazar de Pablo et al., 2019), when specific CHR-P services are available (Kotlicka-Antczak et al., 2020; Salazar de Pablo et al., 2021a).

The effect of baseline exposure to antipsychotics

A recent viewpoint (Raballo et al., 2020) argues individuals with Sarah's symptoms whilst receiving antipsychotics should not be designed with DSM5-APS (or CHR-P) but be regarded as "having antipsychotic medication-attenuated equivalents of first-episode psychosis" (Raballo et al., 2020). Several evidence-based findings question such statement.

Transdiagnostic use of antipsychotics

Antipsychotic treatment does not inevitably indicate the presence of underlying frank psychotic symptoms. Patients like Sarah frequently present with comorbid non-psychotic mental disorders, and antipsychotics (as other psychotropics) are used transdiagnostically to treat other conditions.

For instance, aripiprazole has proven to be effective for Alzheimer's disease with behavioral disturbance or autism spectrum disorder (Solmi et al., 2020). According to available clinical guidelines, aripiprazole 2 mg/die is a valid recommended treatment for Sarah's refractory depressive symptoms (Taylor et al., 2018). Low-dosage antipsychotics, for example quetiapine, are also used off-label (McKean et al., 2018) for bipolar features, behavioral problems, insomnia or anxiety, to the point that antipsychotics have become "a common clinical treatment, irrespective of attenuated psychotic symptoms status" (Gerstenberg et al., 2015). Finally, CAARMS and DSM-5-APS require patients not to be frankly psychotic at the time of antipsychotic initiation.

Minimum effective doses of antipsychotics for a first-episode of psychosis

The antipsychotic effect of these molecules is dose-dependent. For example, Sarah's daily intake of aripiprazole (2 mg) falls well beyond the minimum dose of antipsychotic (i.e. 10 mg), which is effective in first-episode psychosis (Taylor et al., 2018). Previous reports suggest that low dosages of quetiapine (e.g. 25–50 mg/die) are frequently employed in CHR-P individuals (O'Connor et al., 2007). The use of dosages of antipsychotic molecules that do not reach the minimum effective dose is frequent in CHR-P patients: their average level of chlorpromazine-equivalent of 47.6 mg (Gerstenberg et al., 2016) is below the minimum effective dose (i.e. 200 mg) for a first-episode of psychosis (Taylor et al., 2018).

Psychiatric nosography vs treatment guidelines

It has been suggested that antipsychotic medication exposure at baseline should be an exclusion criterion for DSM5-APS (Raballo et al., 2020). Both the DSM and the ICD are diagnostic manuals, not treatment guidelines; DSM/ICD infrequently signpost to the confounding effect of treatments received at baseline. This suggestion oblivions the above real-world clinical issues such as frequent non-psychotic comorbidities and transdiagnostic use of low-dosage antipsychotics. For example, two

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Sarah´s Clinical case

Sarah is a 23 years old lady who works in a barbershop. Sarah's psychiatric and medical history is negative. In recent months, Sarah presented with depressive symptoms of moderate severity and approached her general practitioner, who prescribed her citalopram 40 mg/die, without substantial benefits. Sarah was then prescribed an augmentation therapy with aripiprazole 2 mg/die, which improved her mood. Despite these treatments, over the recent three weeks, Sarah developed the feeling that people around her were staring at her and trying to give her messages; because of these convictions, she felt distressed and found it difficult to concentrate at work. These symptoms were present for about three hours/day, and they did not reach psychotic intensity because she was still able to dismiss them. Sarah's mum became concerned about her mental state and, after finding on the internet information about a mental health service for young people with similar problems (https://www.meandmymind.nhs.uk), referred Sarah's to the team.

Fig. 1. Clinical case.

atypical antipsychotics (risperidone and aripiprazole) have been approved by the FDA for the pharmacological treatment of irritability in autism spectrum disorders (LeClerc and Easley, 2015), which are also frequently comorbid in CHR-P patients (Vaquerizo-Serrano et al., 2021).

Missing those more in need of care

Restricting the DSM-5-APS (or CHR-P) diagnosis to those antipsychotic naïve would decrease the already limited detection power of preventive approaches. Importantly, it may lead to clinical paradoxes, with those individuals more in need of care being excluded (i.e., not accepted by clinical services) from preventive care. Sarah could be excluded from receiving preventive care because she had appropriately been prescribed low dosage antipsychotics for overcoming her refractory depressive symptoms, which added burden to her attenuated psychotic symptoms. Other CHR-P people who may inappropriately be prescribed antipsychotics outside their comorbid mental disorders and at any dosages would be excluded from their much-needed preventive care and left with unnecessary side effects (some of them dose-independent) (Menus et al., 2020; Wijdicks, 2018). This paradox would constrain preventive care to pathways of care, which are idiosyncratic and contingent to local policies, level of implementation of early intervention services and other healthcare parameters. Assigning preventive care based on referral pathways may also be perceived as unethical. For example, disparities in antipsychotic exposures have been documented in ethnic or other disadvantaged patients with schizophrenia (Cook et al., 2015; Lawson et al., 2015). This could lead to the exclusion of individuals at risk from preventive care because of their socio-cultural background.

A pragmatic solution: transdiagnostic assessment and antipsychotic discontinuation

We agree antipsychotics should not be used as the first-line preventive treatment. We also agree exposure to antipsychotics should be carefully recorded in terms of i) reason for prescription, ii) dosage employed, iii) duration (starting and ending date), and iv) impact on presenting features. We suggest that:

1. Baseline exposure to antipsychotics is not set as strict a-priori exclusion criterion because this would constrain preventive approaches to idiosyncratic pathways to care, decrease the detection power of the CHR-P paradigm and cause ethical concerns. Furthermore, this approach would not solve the problems of many young people who might inappropriately be exposed to antipsychotic treatments (but simply ignore this vulnerable group).
2. Specialised services for individuals meeting CHR-P or DSM5-APS criteria should transdiagnostically evaluate whether antipsychotics have been appropriately or inappropriately prescribed.
3. In the case of inappropriate prescription, these specialised services should implement antipsychotic discontinuation approaches. Antipsychotic discontinuation approaches are already being considered in young people with first-episode of psychosis who achieve clinical remission, attain early functional recovery, and have good social support.
4. Discontinuation of antipsychotic medication should be bolstered by complementary treatments such as psychological therapy, routinely offered by specialised services.

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CRediT authorship contribution statement

Dr Fusar-Poli had full access to the study and takes responsibility for the manuscript. Study concept and design: Fusar-Poli; Literature review: Fusar-Poli, Salazar de Pablo; Drafting of the manuscript: Fusar-Poli; Critical revision of the manuscript for important intellectual content: Fusar-Poli, Salazar de Pablo.

Declaration of competing interest

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