The information in this column is not intended as a definitive treatment strategy but as a suggested approach for clinicians treating patients with similar histories. Individual cases may vary and should be evaluated carefully before treatment is provided. The patient described in this column is a composite with characteristics of several real patients.

Making use of N-of-1 trials to treat ADHD in people with psychosis: a hypothetical case

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A 22-year-old man began experiencing auditory hallucinations and paranoid thoughts. His family sought help because of a decline in his academic performance, increased social withdrawal, and odd speech over the last year.

At age 18, the patient had had a single, brief (< 48 h) episode of intense paranoia and grandiose ideas after taking nonprescribed stimulants. He had not been prescribed psychotropic medications in his childhood, and his family had no known history of psychiatric disorders. He responded well to risperidone (titrated from 2 mg/d to 4 mg/d over a period of 4 wk), and after 3 months his auditory hallucinations and paranoid thoughts ceased, though he still had some difficulties at school and strained relationships with peers. During follow-up visits, the patient mentioned that when he was 16, his school counsellor suggested he may have attention-deficit/hyperactivity disorder (ADHD). Upon a full diagnostic assessment, he met the criteria for ADHD and schizophrenia. In addition, a review of his school records revealed several notes suggesting distractibility and lack of attention.

Considering our patient's prior stimulant-induced psychotic episode at age 18, we proposed a carefully monitored personalized (N-of-1) trial to determine the most effective treatment for his ADHD symptoms that would not exacerbate his psychotic symptoms. The chosen intervention was long-acting methylphenidate — a commonly used first-line medication for ADHD — taken once daily at a fixed dose of 10 mg/d.[1] We collected baseline data on his ADHD symptoms using the Adult ADHD Self-Report Scale (ASRS-5)[2] and on his psychosis symptoms using the Positive and Negative Syndrome Scale (PANSS-6).[3] With the help of a pharmacist, similar-looking placebo pills were made for use once daily, and a random, weekly alternating sequence was chosen for a 12-week administration period (concealed from both the prescriber and the patient). A steady dose of risperidone (4 mg/d) was maintained during this period. We followed the recommendations from previous N-of-1 studies in ADHD,[4] but used a fixed dose of methylphenidate to reduce the risk of adverse events in this patient with psychosis. Notably, extended-release methylphenidate needs 10–14 hours for elimination. Once patients and the clinician have a clear idea on the effectiveness and safety of the medication, a higher dose can be started using the highest tolerated dose approach. The patient's family was closely involved with his consent to monitor any exacerbation of psychotic symptoms or any potential adverse effects of the combination treatment, such as extrapyramidal symptoms[5] and tachycardia.[6]

Over the course of 3 months through a weekly telephone interview with the prescribing clinician, we tracked weekly changes in our patient's symptoms using PANSS-6; ASRS-5, modified for 1-week symptoms; and the Clinical Global Impression scale (CGI),[7,8] focused on both ADHD and psychosis. At the end of the trial period, unblinding was done, and the overall impact of methylphenidate versus placebo on ADHD and psychotic symptoms was compared by averaging the rating differences between methylphenidate on and off weeks. The patient showed significant improvement in his ADHD symptoms (ASRS-5 score of 12 when on and 19 when off methylphenidate) without exacerbation of psychotic features (PANSS-6 score of 8 when on and 10 when off methylphenidate, with spontaneity and social withdrawal improving when taking methylphenidate). We decided to continue the methylphenidate treatment, which was later increased to 20 mg/d. The patient has now been on this treatment for nearly 1 year, with no weight gain and with CGI severity scores of 2 for both ADHD and psychosis, indicating sustained remission. His academic performance has improved over the year, and he demonstrates better social engagement.

This case highlights the potential of individualized N-of-1 trials in determining the most effective treatment approach for ADHD in people with psychotic disorders. Emerging literature indicates that methylphenidate is not associated with an elevated risk of psychotic events in adolescents and young adults,[9] even when they have a prior history of psychosis.[10] Despite prescriber hesitance because of the risk of psychotic relapse,[11] larger studies in adults with ADHD and psychosis show that both stimulants and atomoxetine, when combined with antipsychotics, reduce hospitalization rates.[12] N-of-1 trials resolve this therapeutic dilemma in a personalized manner, promoting both prescriber confidence and patient compliance. Implementation of such trials requires multidisciplinary input (pharmacist for blinding, case manager for regular measurements and psychoeducation) within clinical settings, making early psychosis programs an ideal place for these person-centred trials. While the conventional N-of-1 approach could be cumbersome in routine practice, with appropriate consent and therapeutic alliance, it is possible to replace placebo with a lower-dose (ineffective) prescription, use single instead of double blinding when relying on self-report efficacy measures, and reduce the trial period by limiting repetitions to 1 cycle (instead of 3 as described in this scenario)

to achieve optimal individualization of treatments, especially when psychotropic combinations are under consideration.

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