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Antipsychotic Dosing: How Much but also How Often?

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Considerable focus has been devoted to *how much* antipsychotic is appropriate for optimal clinical response, although *how often* antipsychotics need to be administered is also less than clear. Clinicians are aware of the increased risk of relapse related to antipsychotic nonadherence/discontinuation, and current practice dictates continuous antipsychotic exposure with the goal of achieving steady state-levels to maintain effectiveness and prevent relapse. Does this mean we need to (or should) administer antipsychotics at least daily? There is a body of evidence challenging this long-established clinical axiom.

Key words: antipsychotics/dose/dosing schedule/tolerance

D_2 Blockade is the Sine Qua Non of Antipsychotic Activity

Despite efforts to achieve antipsychotic response through other mechanisms (eg, serotonin, glutamate), it remains that *antipsychotic* efficacy so far is hinged to D_2 antagonism. All clinically approved antipsychotics block D_2 receptors, albeit to varying degrees.[1] Neuroimaging studies have confirmed an upper threshold of beneficial D_2 receptor occupancy, in the range of 60%–70%, beyond which chance of response diminishes, while risk of D_2-related side effects (eg, Parkinsonism) increases notably.[2,3]

While D_2 Occupancy is Required, Continuously High D_2 Occupancy is Not

Targeted medication,[4] adherence,[5] and occupancy studies[2,3] have given implicit support to the notion that *sustained* D_2 occupancy approximating this identified threshold is necessary to maintain antipsychotic response; however, this may not be the case. Neuroimaging data have established that over a 24-hour interval, D_2 occupancy levels can fall well below the recommended threshold for at least some oral antipsychotics,[6] as is the case with depot antipsychotics when occupancy levels have been tracked over the duration of their injection intervals.[7]

These findings suggest that 24/7 continuous and high levels of D_2 occupancy are not always required. The scientific question then becomes: What are the implications for antipsychotic administration? In asking this question, we emphasize up front that it is naive to assume a ''one size fits all'' approach to antipsychotic pharmacotherapy. In the end, treatment must be individualized, as response is heterogeneous, from those who require continuous and possibly high doses to those who remain stable even in the face of antipsychotic discontinuation.[8,9]

Non-Continuous Antipsychotic Dosing: Clinical Evidence

Drug Holidays; Intermittent/Targeted Antipsychotic Dosing

As well as dose reduction studies, efforts to minimize antipsychotic exposure related to their numerous and potentially irreversible side effects (e.g., tardive dyskinesia) led to trials incorporating two scheduling approaches. The first was ''drug holidays,'' arbitrarily implemented regular gaps in dosing that ranged from alternate day to 2 months. A review of these earlier studies concluded ''schedules with fewer than four drug-free days a week may have merit in the treatment of chronic schizophrenic patients.''[10] Subsequently, ''intermittent'' or ''targeted'' pharmacotherapy advocated introduction of antipsychotic therapy at the earliest signs of psychotic relapse, with discontinuation between episodes. Critical to intermittent dosing was the opportunity for prolonged intervals off antipsychotics (weeks to months), and it too affirmed the risk of increased relapse and rehospitalization rates with prolonged gaps.[11] As an aside, a significant limitation with this strategy proved to be inability to effectively detect the early signs of relapse.

Extended Antipsychotic Dosing

Drawing upon this earlier work, as well as more recent pharmacological and imaging data, we proposed "extended" antipsychotic dosing based on the premise that clinical response may not be compromised in the face of *fixed, finite* gaps in antipsychotic dosing. Evidence indicates this could provide adequate antipsychotic exposure, at the same time sidestepping the problem of identifying prodromal symptoms that would signal reintroduction of antipsychotic therapy. A pilot study examined gaps of 48–72 hours between doses in stabilized patients with schizophrenia,[12] while a more recent double-blind trial evaluated alternate day dosing over a 6-month interval.[13] No clinical worsening was noted and although subjective reports endorsed benefits, possibly related to diminished side effects, any conclusions in this regard are premature as of yet. The newer antipsychotics have a different profile of side effects (eg, increased liability for weight gain and metabolic abnormalities), and it remains for future investigations to establish whether an extended dosing strategy would translate to advantages that might include these adverse effects.

Might There be Benefits to Non-Continuous Antipsychotic Exposure?

The extended dosing data appear promising, but where does this leave us? Decreased drug exposure is intuitively appealing and potential cost savings cannot be ignored. As of yet though, we lack evidence of clear-cut clinical advantages with such an approach; indeed, one might argue convincingly that taking medication every day is easier to remember. We turn our attention now to findings that suggest continuous vs transient antipsychotic exposure may (*a*) diminish antipsychotic efficacy across time and (*b*) increase risk of side effects (eg, tardive dyskinesia).

Preclinical Evidence

By the 1980s, treatment schedule had been implicated in drug tolerance,[14] and subsequent preclinical investigations soon established that antipsychotic tolerance can occur in the face of continuous treatment. For example, continuous haloperidol treatment resulted in recovery of antipsychotic-suppressed spontaneous motor activity in rats, while this was not observed with alternate day dosing.[15]

More recent studies from our own work have affirmed differences between continuous and transiently high antipsychotic regimens across a number of measures. Continuous haloperidol and olanzapine exposure to rats via osmotic mini-pump vs transient subcutaneous injections results in significantly greater vacuous chewing movements (VCMs, a proxy for tardive dyskinesia in humans) despite higher peak D_2 occupancy levels with transient treatment.[16,17] Similarly, continuous vs transient haloperidol treatment is associated with behavioral dopamine supersensitivity, as measured by increased amphetamine-induced locomotor activity following antipsychotic discontinuation.[18,19] Conditioned avoidance responding (CAR), which has very high predictive validity for antipsychotic activity, is maintained in animals receiving transiently high antipsychotic treatment but diminishes over time with continuous exposure. Finally, the effective dose on these measures was 10-fold lower in the transient-treated animals, suggesting a need for lower doses with transient vs continuous exposure.[18]

There is a small body of preclinical evidence involving endogenous markers that adds yet another perspective. Increases in striatal and limbic homovanilic acid (HVA), comparable to what is seen following acute haloperidol treatment, also occur with alternate day but not with daily haloperidol exposure over time.[15] In a similar fashion, striatal D_2 receptor Bmax, as well as levels of D_2^{High} sites, increases significantly with continuous but not transient haloperidol exposure.[18–20] Conversely, transient but not continuous haloperidol exposure increases c-fos mRNA in the caudate-putamen.[18]

Taken together, data suggest that continuous antipsychotic exposure is linked behaviorally to at least some loss of antipsychotic efficacy (CAR) and behavioral dopamine supersensitivity (amphetamine-induced locomotion upon antipsychotic withdrawal). Neurobiological parallels include decreased HVA, followed thereafter by compensatory D_2 upregulation, as represented by increases in D_2 Bmax and D_2^{High} receptors. Transient antipsychotic exposure, like acute antipsychotic treatment, increases striatal c-fos mRNA expression in the caudate-putamen, suggesting it too may be involved in effecting or maintaining antipsychotic response at the level of gene regulation. In contrast, this is not observed with continuous exposure.

Clinical Evidence

Paralleling the preclinical evidence, are there clinical data to suggest antipsychotic tolerance with continuous treatment? Work with first-episode schizophrenia has confirmed three findings related to antipsychotic treatment: (*a*) response to lower doses; (*b*) sensitivity to side effects; and (*c*) comparatively high response rate.[2,21] In contrast, the more chronic stages of schizophrenia are associated with higher antipsychotic doses and diminished clinical response,[22,23] keeping in mind that the chronic population is more heterogeneous and includes a larger proportion of refractory patients who may be receiving higher doses. While antipsychotic tolerance has been raised to account for a progressive decline in response,[24] nonadherence and/or illness progression are routinely endorsed as more viable explanations. That as many as 25% of individuals on depot antipsychotic therapy relapse[25] tempers the

nonadherence argument, but at the same time does not rule out alternative explanations, eg, a discrete breakthrough episode vs tolerance per se. In contrast, the preclinical description of behavioral dopamine supersensitivity closely parallels the notion of "supersensitivity psychosis" and withdrawal dyskinesias reported clinically, linked to D_2 upregulation as a result of ongoing antipsychotic exposure and observed in the face of drug discontinuation.[26–28]

Discussion

Entertaining any strategy other than continuous antipsychotic exposure in a field where concern over antipsychotic nonadherence is so prevalent seems tantamount to heresy. At the same time, relatively little attention has been paid to the downside(s) of continuous antipsychotic treatment and, as importantly, alternative strategies.

Going forward, what can we draw from the current body of evidence? It appears that continuous antipsychotic exposure is not always necessary, while at the other end of the continuum, intermittent or targeted treatment is not sufficient. Extended antipsychotic dosing, offering transiently high D_2 occupancy within a framework of finite gaps, may represent an effective compromise that sidesteps the negative effects linked to continuous exposure. Further work to confirm these assumptions is needed, but the implications are significant. For example, we have seen in drug development a shift toward extended release formulations aimed at providing continuous antipsychotic exposure; however, this could be moving us in the wrong direction. Similarly, there is renewed interest in depot antipsychotics; notwithstanding differences related to adherence, it cannot be taken for granted that depots will parallel oral formulations in terms of efficacy and/or side effects. Ruling out compounds with shorter half-lives based on the assumption that they require multiple daily dosing would lose its relevance.

At the very least, revisiting how often antipsychotics should be administered will confirm current thinking and practice patterns. It could, though, also fundamentally reshape present guidelines, not unlike what occurred when antipsychotic dosing was examined more rigorously.

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