Determining Clinical Follow-Up in the Context of Widening LAI Intervals:
How Long Is Too Long?

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Long-acting injectable antipsychotics (LAIs) are an essential tool for prescribers who work with individuals with severe mental illness. A recent meta-analysis[1] including studies from research and real-world contexts concluded that LAIs were associated with fewer hospitalizations and relapses when compared to oral antipsychotics. Clinicians today can choose between various LAIs, with injection intervals ranging from every 2 weeks to every 6 months. The dosing interval of an LAI can serve as a strong anchor that influences the frequency of follow-up.[2] The wide range of available injection intervals has raised a clinical question: what is the optimal frequency of prescriber contact for patients with serious mental illness who are treated with LAIs?

Wider injection intervals are preferable to some patients[3] and may theoretically have advantages for the health care system. For example, they may allow a single provider to serve more patients, which could reduce system- and patient-level costs. Given the significant shortage of psychiatrists and other prescribers, which has only been exacerbated by the COVID-19 pandemic,[4] spacing a patient's visits from monthly to every 3 months with a different LAI formulation would essentially triple the reach of our limited workforce.

Another potential approach to extend the workforce using LAIs involves changing the site of injection administration from a clinic setting to a local pharmacy, primary care office, or even the patient's own home using a visiting nurse. While this could theoretically expand care access, authors have also warned that this approach could fragment patient care and result in reduced clinical oversight.[5] We have no good information about the percentage of patients receiving an LAI outside of psychiatric care settings. A pilot study in the United Kingdom[6] has suggested that pharmacist-led chart reviews can identify patients whose injection intervals can be safely widened, even among a population in which "many" patients were receiving their LAI via a visiting home nurse. There are also published reports from systems that adapted to the COVID-19 pandemic by moving patient administration outside of the clinic setting without adverse events.[7]

Whether workforce extension is achieved by widening LAI intervals or changing LAI administration site, the frequency of clinic visits is often based on the injection frequency by default. However, there may be risks to reflexively tying clinical contact to the frequency of medication administration. This approach may have an impact on the therapeutic alliance and provides fewer opportunities to build rapport, intervene on medical comorbidities, or detect early symptom recurrence if longer injection intervals are chosen.[8] Furthermore, we may unintentionally reinforce a reductionist view of the prescriber in a purely biomedical role, overlooking the insight that all medications (including LAIs) are administered in a psychosocial context that shapes their real-world effectiveness. For instance, the choice of a wider spacing interval could have psychodynamic implications for a patient. Because access to wider intervals is gatekept by the clinician, this decision could be interpreted by the patient as a judgment on the status of their recovery, such as if their treatment team feels they are "succeeding" or "failing."

The frequency with which patients are seen in clinical follow-up has largely been left to individual physician judgment without an adequate evidence base to guide such decisions. While very few studies have directly investigated this topic in any medical field, the few studies that have been conducted show significant unexplained practice variation.[9–11] Data from the Veterans Administration (VA)[12] have demonstrated that the scheduling interval has a limited impact on missed appointments, but a robust and linear effect on cancelation rates, which rise from ~20% at 1 month to ~30% by 3 months and ~40% by 6 months. Notably, this effect was most robust for mental health visits, for which the risk of canceling rose to nearly 70% for yearly follow-up appointments.[12] There is at least one prior VA study that attempted to standardize follow-up rates with mixed success in a small sample.[13]

If clinicians offer flexible visits in-between injections (which could be virtual) to address other clinical concerns like substance use counseling, rehabilitation, or medical health independent of injection visits, patients may vote

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with their feet and come in only for their injections. The concreteness of the regularly occurring (and not too infrequent) injection visit may thus be critical, akin to patients' coming to a clozapine clinic for blood work and the intangible benefits from such a routine.[14] On the other hand, a harm reduction model utilizing the longest feasible injection interval may be all that is achievable (ie, when the likelihood of follow-up care is low). Although rarely discussed, less frequent visits could also hold some advantages because overly frequent contact may invite excessive medication changes given the perceived need to "do something." Less frequent interactions concerning court-ordered treatment with LAIs can also unburden treatment staff from this aspect of management, allowing engagement around rehabilitation goals. Future research needs to investigate the reasons that patients fail to show for appointments specifically scheduled between injection administrations. It is possible that patients find these visits unhelpful, and this consumer perspective could inform future recommendations on optimal follow-up frequency. While the recently published European Long-Acting Antipsychotics in Schizophrenia Trial (EULAST)[15] provides preliminary data on the reasons for LAI discontinuation (64% all-cause at 19 months: 17% for lack of efficacy, 13% for safety concerns, and 34% for other reasons), it does not discuss injection intervals or the reasons appointments were missed between administration dates.

In summary, the administration frequency of an LAI provides neither a ceiling nor a floor for the ideal frequency of clinical contact. Although it may serve as a convenient anchor when scheduling follow-up appointments, clinicians should determine the optimal frequency of outpatient visits based on a combination of individual patient risk factors and real-world constraints (eg, limited LAI options because of insurance). Future education efforts should inform both providers and patients of the core message that an injection interval does not dictate the overall frequency of clinical contact. How often a patient is seen in clinic must instead be determined by considering a combination of both drug-related factors (eg, side effects, safety profile, need for metabolic monitoring) and patient-related factors (eg, treatment history, relapse risk, comorbidities, responsiveness to treatment). These drug-related factors should also take into account the other psychotropic medications a patient takes, as these may require different monitoring and dose titration schedules (eg, lithium, valproic acid, or oral antipsychotics added when an LAI achieves a partial response). Between injections, visits may be provided using telehealth or check-ins from allied professionals. As is usually the case in clinical medicine, patient selection is key: for some patients harm reduction will be the best we can accomplish. Our field could benefit from real-world effectiveness data that account for the frequency of clinical contact and the frequency of injections as independent variables. Future investigations are needed to provide empirical evidence to guide visit frequency, and the advent of LAIs of various administration lengths could provide the tool we need to investigate this question. In the meantime, clinics should strive toward offering patient-centered care, with a thoughtfully negotiated mixture of in-person injections, in-person visits, and virtual visits. While this new-found flexibility comes at the expense of an increased administrative burden, the spirit of patient-centered care demands we as clinicians be flexible, too, not just our patients.

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