Lies and LAIs: Why Accuracy of Information is the Key to Understanding the Benefits and the Resistance to Using Long-acting Formulation

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Abstract

There are many lost opportunities to improve outcomes for people with schizophrenia. A striking example is the available evidence showing that using the long-acting version of the same oral antipsychotic is associated with improved longevity. This data has been known for almost a decade yet has had very little impact overall in making LAIs the default approach in services specializing in treatment of psychotic disorders. Instead, oral antipsychotics continue to be mainstay, even for those antipsychotics that have the same agent readily available as a LAI. The relative advantages of LAI over oral will likely widen because advances in formulation technology lead to continued release of better LAIs that address limitations of earlier versions of the LAI. Improvements include ease of administration, rapidity of onset of therapeutic effect, longer injectable intervals, and expanding number of antipsychotics that had only been available as an oral then expanding to include an LAI option.

This paper will offer several hypotheses that attempt to explain some of the underlying reasons for complacency in LAI adaptation. These hypotheses integrate some of the known literature on to is article

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offers several inter-related hypotheses that could explain some of the resistance to LAI adoption. These include 1) not fully appreciating how misinformation pertaining to effectiveness of a current regimen can harm the effectiveness of all future medication recommendations, 2) over-emphasizing LAIs as an adherence intervention without appreciating the true benefit of LAIs over orals is that it is a vastly superior information platform, 3) the extent to which stigmatizing nonadherence is a root cause of patients deciding to withhold information, and 4) failure to appreciate the downstream risks of misinformation as jeopardizing future outcomes. These hypotheses are interrelated and amenable to educational and practice interventions and, if successful, may facilitate more appropriate positioning of LAIs as a default approach to treatment of schizophrenia.

Introduction

While it is beyond the scope of this article to review all the evidence supporting the relative benefits of selecting an LAI formulation instead of its antipsychotic counterpart, I will present a study published a few years ago in Schizophrenia Research (1) to make a point that even strong evidence that LAIs are associated with major outcome benefits compared to the very same oral antipsychotic will languish and for the most part remain ignored and unknown among practitioners and mental health advocates. The authors used the Swedish national health database whose data covers the entire population of Sweden and took a close look at the subpopulation of individuals diagnosed with schizophrenia. They were able to link mortality data with very granular antipsychotic prescription data at an individual patient level between 2006-2013. This made it possible to link exposure times for specific antipsychotic medications prescribed to the risk of death during the prescription interval. This data allowed researchers to compare relative mortality risk for specific antipsychotics that were available as either an oral tablet or as an LAI injection.

The results were stunning. Being on LAIs reduced mortality by 1/3rd compared to the oral version of the same medication. Evey individual oral/LAI comparison showed a lower death rate associated with LAI exposure but taken individually these differences in mortality were not significant. But, when all individual oral/LAI pairs were aggregated into two groups based on oral vs LAI status then *"LAIs ...were associated with 33% lower mortality than equivalent orals."* Equally stunning, at least to me, was the lack of interest in this finding after publication. Think about what that means when a publication shows a treatment that might lower morality by 1/3rd with medications available today that are the same moiety as their oral counterparts. One might be tempted to invoke the uncertainty of any specific study as an explanation for the inertia despite such evidence. But I believe there are other factors at play that, if

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true, would provide an explanation for the snail's pace of change. On some level, I believe many patients and providers are afraid of what will happen to their treatment relationship might happen to the therapeutic relationship. This fear can then be traced to unrealistic expectations concerning medication adherence as a requirement for a good working alliance. As covered below, this paper will get into the evidence supporting this theory. Before turning to LAIs, let's discuss

The problem of poor information

Many of the hypotheses that follow have to do with missing information or misinformation as being a major barrier limiting outcomes in schizophrenia. Remember that the nature of schizophrenia makes it unlikely that the initial medication regimen addresses all symptoms and has no side effects. Instead, over the course of the illness, patients will try different medications, and the outcomes from these experiences provide an individualized information platform that can be used for subsequent treatment decisions. Likewise, another information platform is developed based on behavioral patterns exhibited in the person's coping styles, including complications like rejecting medications or continued use of substances that attenuate efficacy of prescribed medications. Knowledge gained about the individual will evolve and grow over time. If known and communicated, this knowledge can be used to inform current and future medication recommendations. Invoking Bayes theorem to justify using a priori information to improve probability of favorable outcome is a technical way of saying that our future treatment results depend in large part on what is learned from past treatment outcomes. The ideal scenario is to have a comprehensive information base covering the treatment history, including dosage, duration, response, tolerability, along with information on complicating behavioral factors such as medication adherence. The latter information is incredibly valuable when assessing whether the poor response is from inherent efficacy limitations of the medication or is better explained by other factors such as undisclosed nonadherence. The problem is that within the context of US treatment services, this kind of information rarely accessible. It is lost, incomplete or scattered, making it unusable for future treatment planning. The clinician or team will usually have a medication plan that is deemed acceptable and tends to be the automatic "go to" medication choice. This is understandable but limits the opportunities to choose therapies based on prior learnings for that individual patient. When this keeps happening again and again with the same patient, it feels like watching the movie "Ground Hog Day" where the character wakes up on the same day over and over.

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What is holding back LAIs to be default treatment approach for schizophrenia?

As LAI options and formulations have advanced, it becomes much easier to place LAIs as the default way to treat schizophrenia, especially when it is an option instead of the oral counterpart. This shift in making the LAI the default has not happened, and this section will present 3 hypotheses that may explain some of the headwinds in LAI adaptation.

Hypothesis 1: Complacency about lack of information

Missing or fragmented information about prior treatment history is the rule not the exception when treating schizophrenia. Starting medication without prior knowledge despite years of prior treatments is a status quo practice, resulting in lost opportunities to have the knowledge base needed to help guide strategic medication decisions. Busy clinicians will lean towards choosing among a handful of default oral antipsychotic options and leaving it at that. On a day-to-day workload basis, there is little incentive to lean into embracing the information advantages from changing the default *formulation* from the routine oral to its LAI counterpart, representing only one of many lost opportunities to use prior information to inform current and future medication recommendations.

While *missing* information is bad enough, *misinformation* is even worse. Misinformation is defined in the context of this discussion to be the result of a decision on the patients' withholding key information (usually nonadherence) between what was prescribed and what was actually taken. The clinical team then acts on the incorrect assumption that the medication was taken as prescribed and use this misinformation to guide treatment recommendations. Using an analogy of driving to a new location with your phone's GPS illustrates the difference. A GPS that stops working because of a dead battery is annoying but not misleading. A GPS program that looks like it is working but has programming errors that send you in the wrong direction is misleading. Misinformation leads to poor decisions; applied to treatment of schizophrenia, it can result in choosing the wrong medication or wrong dose. Unfortunately, there are strong incentives for both patients and clinicians to interact in ways that perpetuates misinformation, which is covered in detail in hypothesis 3.

Hypothesis 2: LAIs are oversold as adherence interventions

For generations of clinicians, the primary reason to use LAIs over oral antipsychotic was as an adherence intervention.(2) Since then, the concept of uses of LAIs has broadened(3), but many practitioners still hold on to the older concept of reserving LAIs to patients identified as nonadherent to oral therapies. In fact, even now, many educational programs on LAIs continue to highlight their potential as adherence

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interventions. For example, an excellent CME overview published in the 2024 discussed LAIs as follows; *"Given the high frequency of nonadherence in schizophrenia... long-acting injectables have obvious advantages for long-term treatment…"* (4) Such a statement can be understood as saying that LAI's benefits come straight from better adherence, an assumption that oversells LAIs as adherence "fixes". Clinicians who are not very experienced in LAI might interpret these statements that LAIs will solve adherence problems for patients who don't accept [oral] medication. The reality is very different. As shown in clinical insert #1, overselling LAIs at the front end of training may lead to abandoning LAIs out of disappointment. Figure 1 provides an alternative visual model that emphasizes information advantages of LAIs. I believe this model is more realistic and clinically useful. Understanding LAIs as superior to oral as an information platform is more accurate and makes it easier to match the objective of starting an LAI to the specifics of the individual patient. As implied by Figure 1, LAIs are *always* better than oral medications on quality of information but only *sometimes* improve adherence.

Case vignette 1: LAIs are more likely to succeed as information platforms

Case history: An acute inpatient unit decided to initiate LAIs before discharge for their "revolving door" patients in the hopes of lowering 1 month readmission rates. After staff training, the first patient started on an LAI before discharge was someone well-known to staff due to multiple readmissions. He accepted his 1st LAI a day before discharge and was scheduled for his second LAI to be given at the time of his outpatient appointment 4 weeks later. He did come for his outpatient intake and but did not receive his second injection and then was lost to follow-up until coming back to the inpatient unit.

Was the LAI a success or failure? If the expectation was that he'd stay on his LAI long-term, then the LAI intervention was a failure. If expectation was to use LAIs to help transition to outpatient care while getting him started on a new treatment approach, then the LAI intervention was a success.

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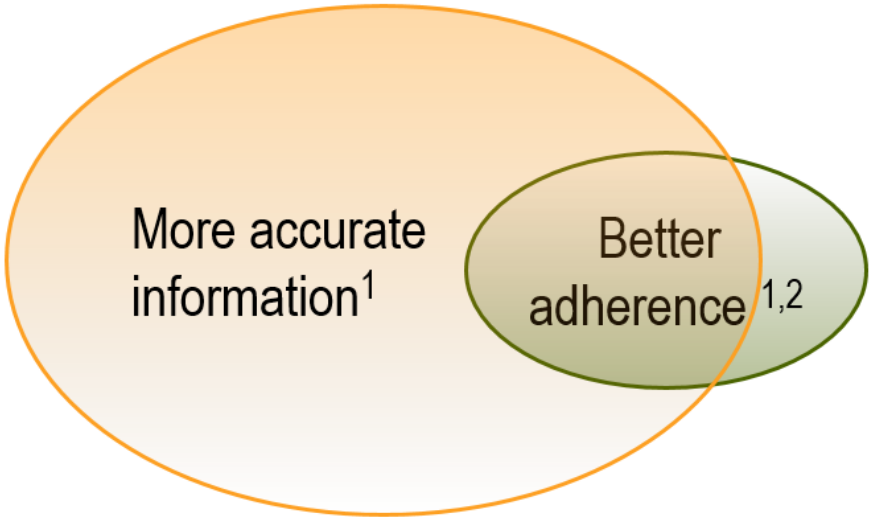
Figure 1: LAIs information advantage > direct adherence benefits



[1] conceptual model comparing magnitude of benefit of better information relative to direct adherence benefits

[2] shows that adherence benefits not as common as information benefits and that most of the potential adherence benefits are related to information advantage

Weiden, P. J. (2016). Redefining Medication Adherence in the Treatment of Schizophrenia: How Current Approaches to Adherence Lead to Misinformation and Threaten Therapeutic Relationships. Psychiatric Clinics of North America.

Hypothesis 3: Fear of disclosure causes and perpetuates misinformation.

"Everyone Lies" Greg House from TV Series House, MD(5)

Why do patients lie about their adherence? In the long run, it is not in their own best interest given the likelihood that misinformation might jeopardize the effectiveness of subsequent treatments. When phrased this way, one answer is that most patients are not thinking about how this may impact their future treatment plan. It is much more likely that "withholding" or "lying" is based on social norms that are in play with the clinical team. Disclosing nonadherence risks disapproval or worse. This issue was hard to find in research literature specific to schizophrenia disease states but can be found for other disease areas. One study found that patients often failed to disclose the reality of what they were taking primarily because of the desire for social approval (being seen as a "good patient") or the fear of social consequences (e.g. perceived or actual rejection or social disapprovals). (6)Given the challenging life circumstances among people with schizophrenia, it would seem likely that the social penalties of

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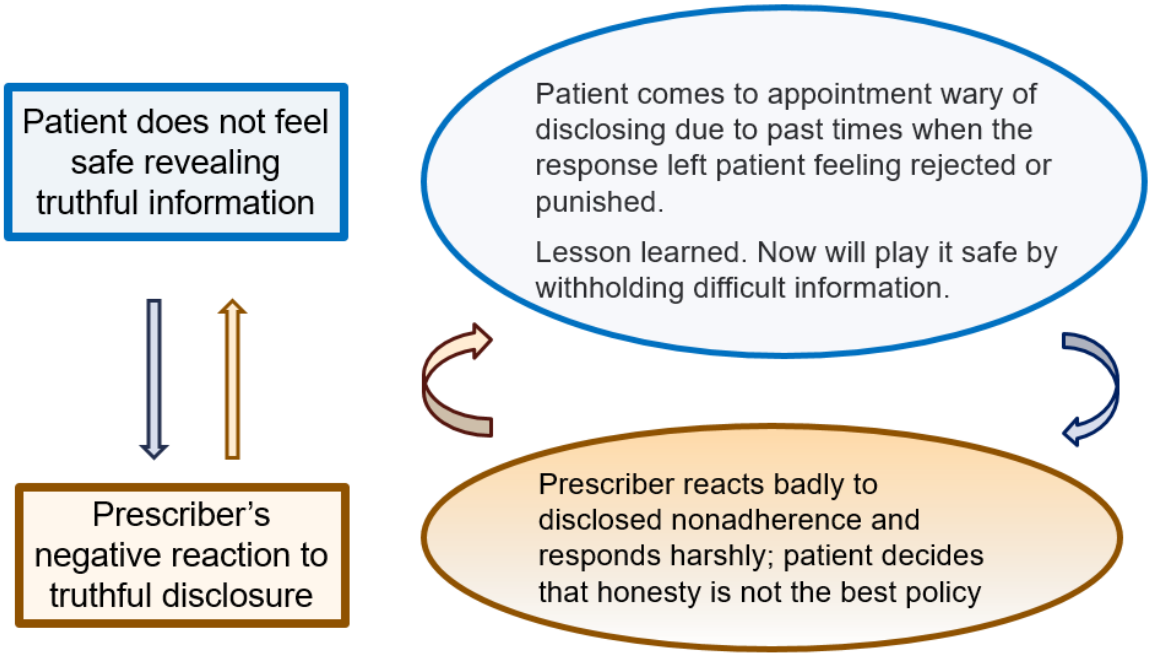
disclosing information that might annoy their clinicians would on average be greater than medical conditions. Based on my clinical research in this area, many patients with schizophrenia have learned the hard way that nothing good comes from truthful disclosure of unwelcome information such as nonadherence. (7-9) Also, the same qualitative research found that a common response of well-meaning clinicians when first learning of nonadherence from their patient is to immediately go into reciting reasons why stopping medication is a bad idea. Unfortunately, this response preempts the opportunity to actively listen to the patient to better understand the patients' perspectives on medication. Although well-meaning, going into lecture mode will likely be experienced as the clinician being out of touch with what matters to the person. Figure 2 is a visual depiction of how these interactions can devolve and exacerbate the disclosure problem as the discussion is unpleasant to all. The quick fix is for the patient to withhold the truth and for the clinician to turn a blind eye to what is really happening. Accurate information is sacrificed and eventually the patient pays the price of misinformation that compromises future medication decisions.

Figure 2: Relationship Barriers to Truthful Disclosure of Undesirable Information



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Putting these together

The above hypotheses, taken together, may help explain some of the reluctance to adapt LAIs in routine practice. Patients who make a decision to stop antipsychotic medication do not want to be lectured, scolded. or ignored from honest disclosure of their decision. Instead, they hope that just this time they can keep it all under wraps and maybe this time they will be fine without medication. It follows that the desire to bury honest disclosure is the main reason to reject LAIs out of hand. The same reluctance in LAI use might be more likely for clinicians who do not want to deal with nonadherence or would rather not know about the extent to which undetected nonadherence is happening on their clinical caseload. If true, it may feel self-righteous to criticize these clinicians for their passivity. But there is another side to this story. Some educational programs on LAIs can seem to come down harshly on practitioners who avoid LAIs. In my opinion a better strategy is to detoxify the topic of adherence and to teach practitioners more effective ways to work with their patients on these issues without poisoning the topic or the therapeutic relationship. It is my belief that paying attention to these issues will help move the field to accept LAIs as the default approach instead of orals. Implementation of LAIs would likely come after - not before - we change the way we work with our patients on their adherence concerns within the broader framework of nurturing the therapeutic relationships (10). Continuing with the status quo will fail as the status quo perpetuates these dysfunctional interactions between patient and clinician. The next section proposes three action items for consideration as action items for the field.

Action item 1: Focus more on the need for accurate information.

Many clinicians have become so accustomed to missing and misinformation that they forget about the potential to improve outcomes. It seems to me that the field has not adequately identified this as a key target for quality improvement. Admittedly this topic might not be as exciting as discussing new medications and new mechanisms. But the tedious task of accurate information is a foundation forgetting best outcomes with our medications. In context, it seems to me that information platforms are even more important than ever as new therapies become available. Emphasizing the need to support accurate information platforms is a natural starting point for discussing the use of LAIs. In fact, it seems to me that the argument for routine use of LAIs is, in many ways, part of the broader need to improve access and accuracy of treatment information for any person facing a long journey of recovery from schizophrenia (11) It seems that the barriers to accessing medical records on digital platforms such as EPIC can be modified for persistent severe psychiatric disorders.(12) LAIs are an important tool in such efforts but their use will be more effective with coordinated efforts to improve other methods to support

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information platforms. Shifting the spotlight away from adherence benefits to the broader case of supporting better information platforms makes it easier make the case for LAI versions to take first position before their oral counterparts.

Action item 2: change interactions in ways that remove incentives to lie.

LAIs will never become mainstream as long as patients remain incentivized to lie and clinicians remain stuck in taking nonadherence personally. Whatever you call it – lying, withholding, nondisclosure – absolutely needs to be de-toxified in a way that patients will feel free to openly disclose nonadherence without having worry about the consequences of honesty. Clinicians need to better understand the immediate and lasting damage that come from reacting to nonadherence in a way that puts distance between the patient and the clinical team. (13, 14)Instead of reacting with irritation or going into pedantic lecture mode, it is much better to make this a point of discussion where the clinician learns from the patient more about the experience and show gratitude that the patient felt safe enough to take the emotional risk of disclosing such information. Insert 2 presents a dramatic example of what can happen when the clinician inadvertently gave a patient a strong incentive to lie about adherence after it happened.

Insert 2: How relationships matter when using or eschewing LAIs

Feedback on why LAIs would threaten a therapeutic relationship

After a talk on LAIs given in a weekly PGY3 psychopharmacology course, a resident told me of a major concern she had with LAIs and why she did not use them in her medication clinic. She admired the work of Carl Rogers and the principles of client-centered therapy, which is based on what Rogers called “unconditional positive regard” for all patients. She felt that the principal of unconditional positive included showing trust and this trust included being able to truthfully inform her of any problems, including going off medications. Her perspective was that offering LAIs would be a signal to her patients that she did not trust regarding medication management issues or disclosing adherence problems.

Follow-up on a relapsing patient

A few months later, she told me about one of her cases that helped her re-evaluate her concept of trust. One of her schizophrenia outpatients was admitted with acute psychotic symptoms and eventually told the inpatient team that he had stopped his medication a few months back. This happened after experiencing sexual side effects. He planned to tell his doctor but held back and then

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avoided it completely so he would not “hurt her feelings”. He asked the inpatient resident to tell her what happened and hoped that she would continue to see him even though he was a “bad patient”.

Lessons learned

In many ways, this resident was to be commended for her dedication and willingness to learn. It seemed to that in hindsight the failure to report stopping medication was not due to the therapeutic relationship directly, but rather the undue focus on ”trust” as a requisite for a positive therapeutic relationship. Although she set criteria for herself (eg no LAIs), the focus on “trust”, made it harder for the patient to disclose stopping medication in a timely manner. At first, he did not feel comfortable disclosing sexual side effects. But after he hesitated, it was worry about “trust” that was the main cause of remaining silent about going off his medication.

Action item 3: Focus on LAIs as superior information platforms

As stated above, if most of the benefits favoring LAIs can be linked to information advantages, would it not make more sense to present the use case for LAIs this way. Current practice often leaves clinicians searching for ways to recommend LAIs, and they frequently “choke”. Unlike the 2007 APA guidelines for treatment of schizophrenia that emphasized LAIs for adherence, the 2020 APA treatment guidelines broaden the use case to other possible benefits that go well beyond adherence to include using LAIs as a preferred method to determine true pharmacologic treatment-resistance from other causes of persistent symptoms. An LAI trial, if accepted, eliminates the risk of misinformation of undetected poor adherence to oral medication, making the LAI trial a safer way to accurately recommend clozapine. It seems this rationale for clozapine selection can generalize to many other situations, and it shifts the LAI discussion away from “We are recommending this LAI to help your adherence” to “we are recommending an LAI to give us much better information about what medication might be best for you” Table 1 below summarizes some approaches to detoxifying adherence discussions to make them much more collaborative than what is often practiced today.

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Table 1 Achieving psychological safety in adherence or LAI discussions

Approach	Implementation
Unconditional acceptance of nonadherence when disclosed and genuine interest in reasons [1]	As per Carl Rogers , inform and model in interaction unconditional positive regard and acceptance of disclosing nonadherence [2]
Understanding and acceptance of why patients choose to withhold important information	Start with orienting patients as to how you will manage disclosing nonadherence. Encourage honest communication as your request even if it means revealing behaviors that might be ill-advised
When learning about nonadherence, use active listening and delay feedback	Use this information as an opportunity to better understand the patients perspective. Your opinion can wait until later.
Discussion of LAI should be patient-centered focusing on collaboration over coercion, and link to personal goals	It is usually better to reframe the LAIs as an information platform and acknowledge that patients can stop LAIs without social penalty
Present LAI as a more reliable way than the oral version to assess a new medication	It is easier to make an LAI recommendation by framing the information advantages with shared goal of achieving efficacy without major side effects, and that misinformation poses safety risks
Emphasize information advantage of LAIs for long-term recovery planning	• Inform patients that LAIs help guide better medication decisions • let patient know it is an experiment try out; starting an LAI does not mean staying on it

[1] Weiden, P. J. (2011). The adherence interview: Better information, better alliance. Psychiatric Annals 41(5): 279–285.

[2] Oberreiter, D. (2021). The evolution of Carl Rogers' thinking on psychosis and schizophrenia Person-Centered & Experiential Psychotherapies 20(2): 152–173.

Summary

This article attempts to address why LAIs continue to be a second thought while oral formulations continue to be the default approach to treat schizophrenia. The argument that not all orals are available as LAIs, while true, cannot explain why LAI use still lags behind orals when both are available.

The first is the misconception that the main use of LAIs is to improve medication adherence. This overplays LAIs as some kind of automatic adherence fix. It misses the broader concept that when LAIs do improve adherence, it is often by providing better information than would be possible with orals. The second issue covered is the damage done by misinformation that comes from withholding information about nonadherence. (15-17) The root cause for misinformation is that patients prioritize the therapeutic relationship and want to avoid the possible consequences of being a "bad patient". Clinicians

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may also tacitly accept nondisclosure to avoid dealing with being blindsided by this information. In doing so, both patients and providers interact in ways that show that being seen as a “good patient” is a priority. (18, 19) Left on the back burner is the fallout of misinformation that jeopardizes future outcomes.

The answer to these barriers is easier once identified. Better education on how information can help, or harm outcomes is needed, as is training on how the therapeutic relationship can help or hinder LAI acceptance. Most important is to move away from the problems caused by focusing only on adherence while ignoring the broader issues. It is my opinion that LAIs implementation will be much easier once the toxic effects of adherence as bad behavior is banned from clinical interactions. Addressing these issues may help clear a path towards shifting from an oral antipsychotic to its LAI counterpart as the default approach.

Competing Interests:

Consultant: Alkermes, Abbvie, Anavex, Boehringer-Ingelheim, Bristol Myers Squibb, Delpor, Luye, Maplight Therapeutic, Serina Therapeutics, Teva, Vanda

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