Long-Acting Injectables with Dr. Cummings

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In today's episode of the podcast, we discuss the use of long-acting injectable (LAI) antipsychotics. LAIs are administered in intervals ranging from every 2 weeks to every 6 months, eliminating the need for daily oral antipsychotics and thereby improving adherence.

When are long-acting injectables helpful?

The most notable advantage of LAIs is improved adherence compared to oral formulations. In Europe, 40-50% of patients experiencing psychosis are treated with LAIs (Watts, 2014). In the U.S., the rate can be as low as 10% of treatments (Kane et al., 2021). This is unfortunate, as one of the main reasons for relapses is non-adherence to the oral medications (Robinson et al., 1999; Caseiro et al., 2012). For oral medications, adherence rates are extremely low, often approaching ~1/3, even including a 'fudge factor' (classifying 80% adherence as adherent) (Valenstein et al., 2006). There are a number of factors that might contribute to this, including adverse effects and impaired insight into one's own symptoms (anosognosia).

A benefit to injectables is they do not require a daily adherence schedule. There are formulations of paliperidone palmitate that can be administered as infrequently as every three or six months. Additionally, noncompliance may be less of a concern with LAIs since they cannot be hidden ("cheeked") or spit out.

A number of studies demonstrate LAIs are associated with lower rates of relapse, hospitalization, and mortality. Perhaps most notably, a Swedish study by Taipale et al. of 29,883 birth-death records showed that, over the course of 7 years, those taking LAIs had a 33% lower rate of all-cause mortality (including death by suicide, accident, overdose, violence) than those taking the equivalent oral counterparts (0.67, 0.56–0.80) (Taipale et al., 2018).

Injection Tips

It is important for psychiatrists to know how to administer these medications to their patients. Adherence is more likely when patients do not have to make a third-party appointment with a provider they may or may not trust.

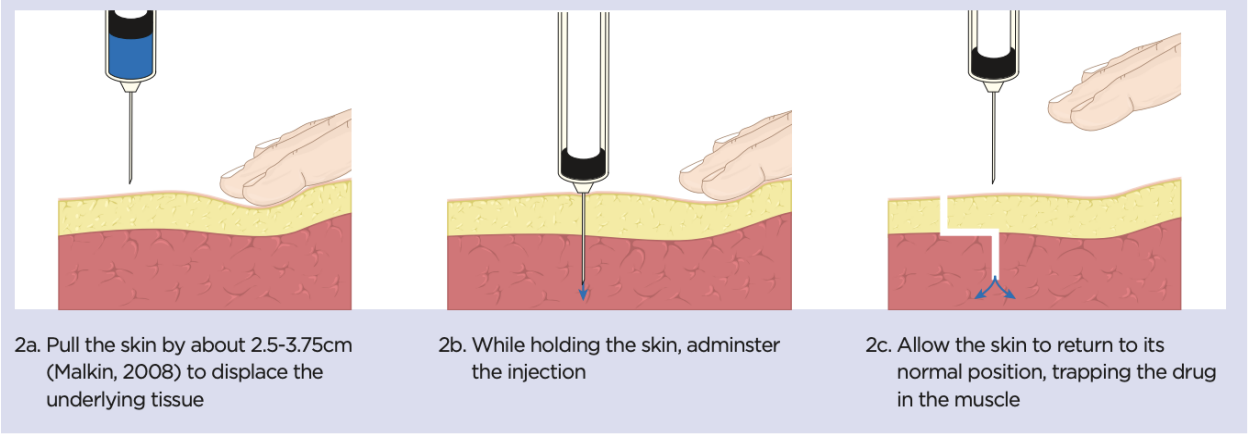
Long-Acting Injectables with Dr. Cummings

Vardaan Bhat, Michael Cummings, M.D., David Puder, M.D.

Nurses deliver injections regularly and can teach this skill very quickly. For the saline-based LAIs, the injection is usually straight in the gluteal or deltoid muscle. The needle goes in and is drawn back slightly (to make sure it's not in a blood vessel), injected, and pulled out.

For first generation oil-based LAIs such as haloperidol decanoate and fluphenazine decanoate, the Z-track method is used, which involves pulling the skin & subcutaneous tissue while injecting and releasing them afterwards. This prevents the needle from leaving a continuous passageway from muscle to subcutaneous tissue, sealing the medication in the muscle. It leaves behind a viscous liquid material that slowly releases medication into the bloodstream over time. Many of these injectable medications last for a month or more, depending on the drug.

Figure 1: Z-track technique (illustrated)



Note: from Shepherd E (2018) Injection technique 1: administering drugs via the intramuscular route. Nursing Times [online]; 118: 4, 23-25. This article was updated by Shepherd E on 9 March 2022.
https://www.nursingtimes.net/clinical-archive/assessment-skills/injection-technique-1-administering-drugs-via-the-intramuscular-route-2-15-03-2022/

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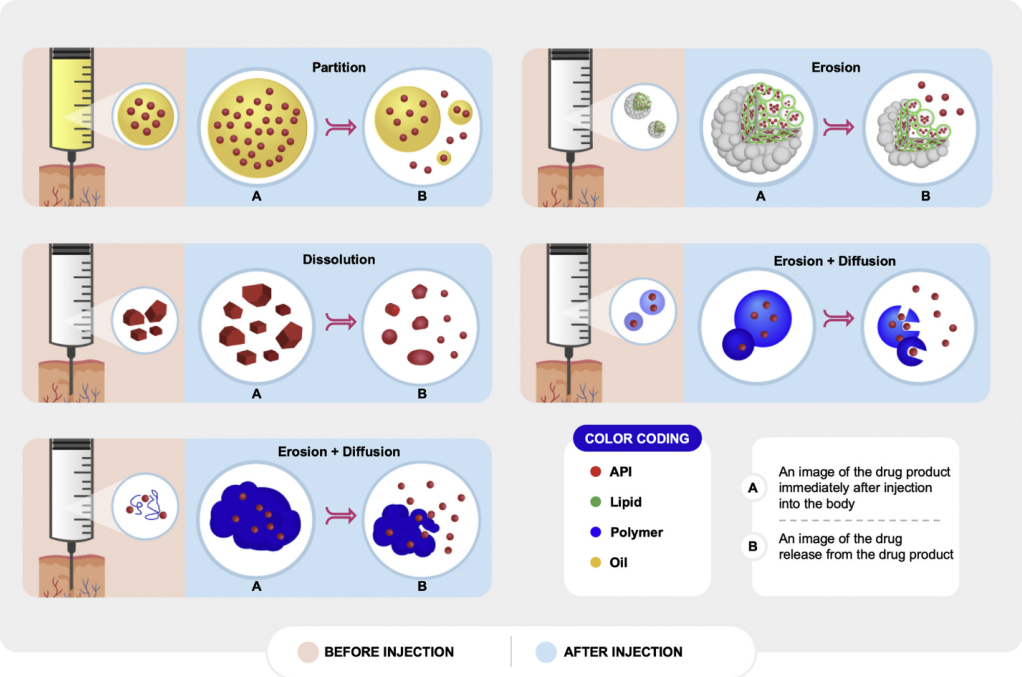
Vardaan Bhat, Michael Cummings, M.D., David Puder, M.D.

How LAIs Work

Figure 2: Ester LAI antipsychotic disposition



Five LAI technologies are displayed, from top to bottom, left to right: oily solutions, suspended solids, ISF polymer implants, MVLs (or other liposomes), and er microspheres. For each technology, the panel is split into two parts showing before injection (left, red) and after injection (right, blue). Before injection, the DP is shown in a syringe with an inset showing the structure of the DP in solution or suspension. After injection, the DP is shown immediately after injection in the body (A) and after API has been released (B), with the primary mechanism of release displayed above. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Note. from O'Brien, M. N., Jiang, W., Wang, Y., & Loffredo, D. M. (2021). Challenges and opportunities in the development of complex generic long-acting injectable drug products. Journal of Controlled Release, 336, 144–158. https://doi.org/10.1016/j.jconrel.2021.06.017

Decanoates are bonded to a 10-carbon lipid chain that is suspended in sesame oil, which is injected into the belly of the muscle where it forms a small sphere and gradually releases the medication. In fluphenazine's case, the most common dose interval is 2 weeks. For haloperidol, the dose interval is usually 4 weeks.

With drugs like paliperidone palmitate, a microcrystal suspended in saline is injected into the muscle, where it slowly dissolves. The reason they last a month is that the tiny crystals dissolve

quickly and release the medication early, while the bigger crystals dissolve more slowly and provide the later dosing of the drug. Formulations of paliperidone palmitate with even larger ranges of crystal sizes last three and six months, respectively.

There is also a version of depot risperidone with microspheres, similar to crystals, that is bonded to a polymer that dissolves.

Two LAI formulations of aripiprazole include aripiprazole monohydrate, which is a crystal, and aripiprazole lauroxil, which is a different type of crystal and has longer variability in terms of how slowly it can dissolve.

There is an LAI formulation of olanzapine pamoate that is bonded to a salt crystal. One version is dosed every 2 weeks and another is dosed every 4 weeks.

In short, the idea is that once these medications are in the muscle, they stay there and, by one mechanism or another, slowly release the drug into the bloodstream.

When are LAIs not useful?

LAIs are not contraindicated in any situation where an antipsychotic is appropriate to use. It is advisable to wait to start an LAI until it is certain the person responds to the medication and tolerates it well.

The biggest caveat is that the elimination half-life is incredibly long. If an LAI is administered and it does not work well, the patient will have to wait 5 half-lives. In the longest case, Invega Hafyera (paliperidone palmitate), designed to last 6 months, will require 30 months for wash-out. Others have half lives from 21-46.5 days, so wash-out is still very long.

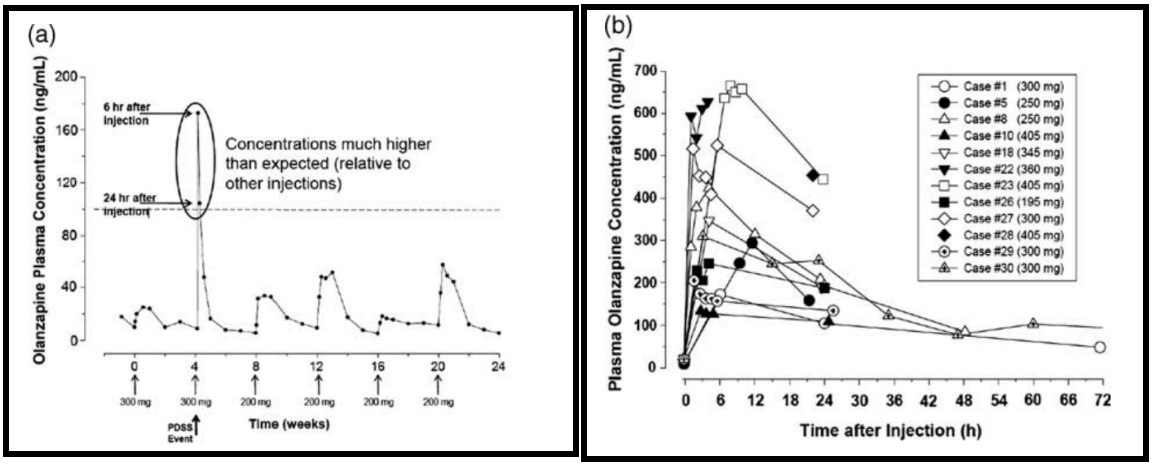
Risks

Unlike the others, olanzapine has a small but nonzero (0.1%) risk of rapid release. The FDA requires that patients be watched for three hours post administration to monitor for sedation via rapid release.

If the olanzapine LAI does release rapidly and a patient becomes very sedated, they should be observed until they wake back up and have their vitals taken. They've essentially received an overdose of the drug.

Because of the rapid-release warning, olanzapine pamoate is not often used. The risk of rapid dissociation doesn't exist for any of the other LAIs.

Figure 3: "Kinetic profiles of severe sedation cases with olanzapine pamoate. (a) Single detailed case example, (b) multiple examples." (Meyer, 2013)



Note. from Meyer, J. M. (2013). Understanding depot antipsychotics: An illustrated guide to kinetics. CNS Spectrums, 18(s1), 55–68. https://doi.org/10.1017/s1092852913000783

Side Effects of LAIs vs. Oral Counterparts

It is suggested that LAIs may have comparable or improved tolerability relative to their oral counterparts, since LAIs lack the sharp peak plasma concentration & peak-trough ratio seen in oral medications.

Long-Acting Injectables with Dr. Cummings

Vardaan Bhat, Michael Cummings, M.D., David Puder, M.D.

Transitioning From Oral to LAI

Switching from oral to long-acting injectable (LAI) antipsychotics may require a loading dose to reach steady state more quickly. The specific loading and maintenance doses vary depending on the LAI being used.

Haloperidol decanoate:

- Such a slow climb that if started and given every month, it would take 3-5 months to reach steady state.
- This is overcome by loading the drug. E.g., switching from oral 20 mg haloperidol daily and loading it at 200 mg/week for 3 weeks.
- The oral medication can be stopped when the second loading dose is given. The maintenance dose can be started 14 days after the second loading dose, then 20x original dosing once a month. E.g., 400 mg haloperidol once a month, usually administered 200 mg every 2 weeks due to volume issues.

Fluphenazine decanoate:

- Very similar to haloperidol decanoate.
- Usually loaded at 25-50 mg a week for 3 weeks and continued at a maintenance dose starting 2 weeks after the last loading dose.
- 10 mg a day orally ~= 12.5-25 mg fluphenazine decanoate.

Paliperidone palmitate:

- The starting point is a monthly dose (INVEGA SUSTENNA) because the INVEGA TRINZA (every 3 months) and INVEGA HAFYERA (every 6 month) are intended for people who have already responded to and are stable on the monthly injection (due to extended washout from longer-acting formulations).
- Usually start with 156 mg or 234 mg as the initial injection.
    - 1 week later, depending on target blood levels, another dose of either 156/234 mg
    - Then simply continue every month.
    - One limitation:
        - 234 mg/month is equivalent to ~4.5-5.5mg/day oral risperidone.
        - If a patient required >4.5-5.5mg/day oral risperidone, they may have difficulty using INVEGA SUSTENNA because the corresponding LAI dosage can’t be achieved within the recommended dose range.

- The number of doses can be increased beyond the recommended dose range, but this becomes prohibitively expensive because of the proprietary nature of the drug.
  - Cost comparison:
    - Haloperidol decanoate and fluphenazine decanoate have a wholesale cost of less than $500 per year.
    - The wholesale acquisition cost at max dose for INVEGA SUSTENNA is ~$25,000 per year.

Risperidone (2 LAI formulations):

- RISPERDAL CONSTA (with oral crossover for 3 weeks, as it doesn't start dissolving until then)
  - Injected every 2 weeks
- RISPERIDONE PERSERIS (subcutaneous formulation): comes in 90 mg and 120 mg doses
  - Roughly equal to 3-4 mg/day oral Risperidone
  - Doesn't require oral crossover.

Aripiprazole (2 LAI formulations):

- Aripiprazole monohydrate/ABILIFY MAINTENA:
  - Give an initial injection of 300-400 mg and continue half the oral dose for 2 weeks.
  - In a lot of countries outside the US, they've replaced this with a second injection after 1 week, followed by maintenance treatment.
- Aripiprazole lauroxil/ARISTADA INITIO:
  - Give an initial dose of ARISTADA INITIO (rapid-release formulation of ARISTADA) and then start the maintenance medication a week later.
  - Doesn't require oral crossover.

Olanzapine pamoate (ZYPREXA RELPREVV):

- No oral crossover required
- Two possible dosing intervals: once every 2 weeks and once every 4 weeks
- Note risk of rapid release, as discussed under "Risks"

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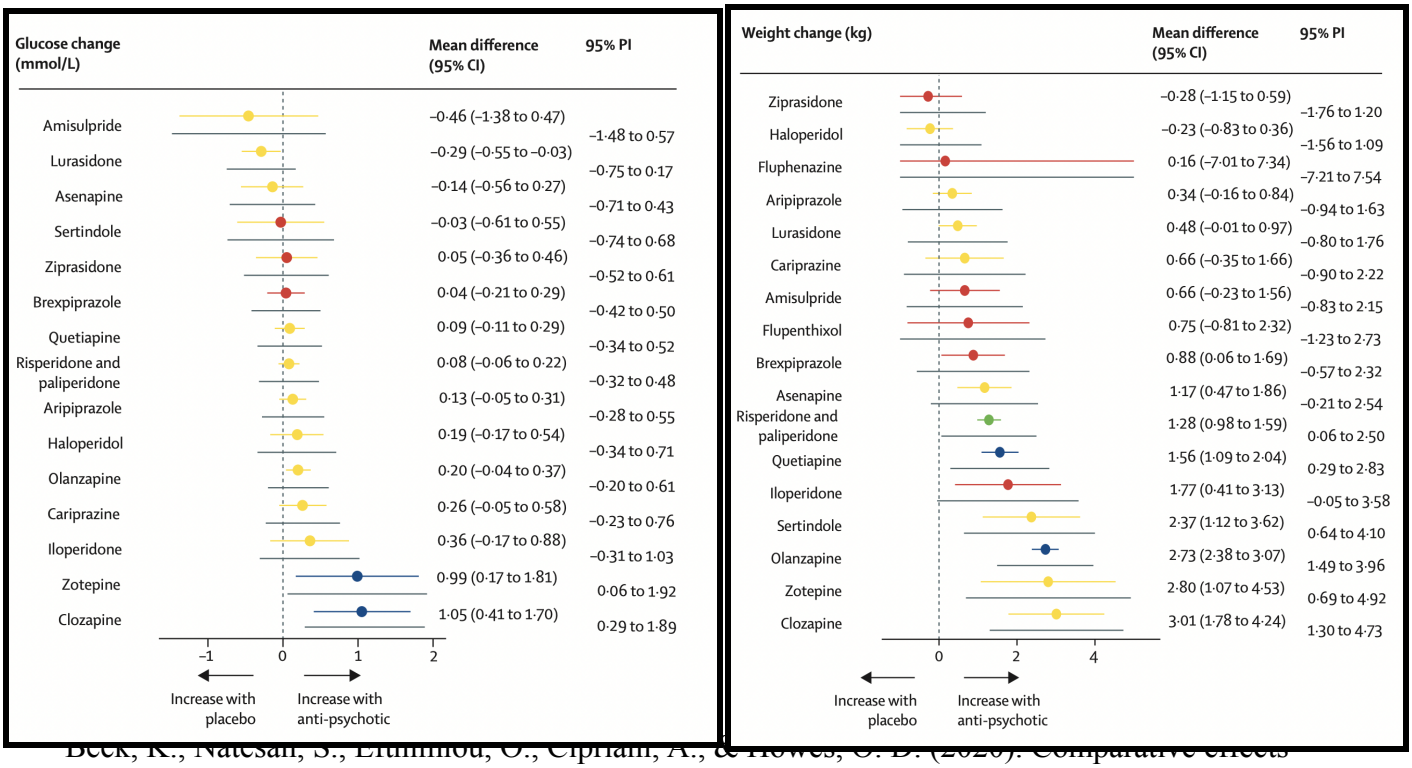
Metabolic Dysregulation

A meta-analysis by Pillinger et al. in 2019 looked at comparative metabolic changes from taking 18 antipsychotics combining 100 randomized trials in 25,952 patients for predictors of metabolic dysregulation and associations. In regards to weight change, ziprasidone and haloperidol were lower risk whereas quetiapine, olanzapine and clozapine were high risk.

Figure 4: Forest plots of glucose and weight change in patients using antipsychotics



Beck, K., Natesan, S., Efthimiou, O., Cipriani, A., & Howes, O. D. (2020). Comparative effects of 18 antipsychotics on metabolic function in patients with schizophrenia, predictors of metabolic dysregulation, and association with psychopathology: A systematic review and network meta-analysis. The Lancet Psychiatry, 7(1), 64–77. https://doi.org/10.1016/s2215-0366(19)30416-x

Limitations of ziprasidone are that it is not available as an LAI, it is difficult for GI tract to absorb, and has to be taken proximate (within 30 minutes) of a 500 calorie meal; otherwise,

absorption is 50% or less of what it would be. Also, looking at other meta analyses, ziprasidone tends to end up at or near the bottom in terms of efficacy.

Managing Metabolic Syndrome and Weight Gain

It is suggested that psychiatrists have not been nearly aggressive enough in intervening to prevent or treat metabolic syndrome.

- Criteria for proactive metabolic treatment:
  - Family/personal history of obesity
  - Weight gain of:
    - 5% or more in first month of antipsychotic use
    - 7.5% in first 2 months
    - 10% (or increase in BMI of 1) in first 6 months

- Most common preventive agent against metabolic syndrome:
  - Metformin
    - Increases insulin sensitivity
    - Not very prone to cause hypoglycemia
    - Does a very nice job of preventing AP-associated weight gain and glucose intolerance.
    - If someone has already gained weight and they are already glucose intolerant, the metformin ceases to be very effective.

- A new class of med being used in circumstances where it's not appropriate to switch antipsychotics is the glucagon-like peptide-1 (GLP-1) receptor agonists.
  - Liraglutide is the most studied in psychiatry.
  - Several GLP-1 agonists available on the US market:
    - 6 injections, 1 oral form.
    - In most studies, ~⅔ of people achieve normal glucose tolerance.
    - People also tend to lose about 10-30% of baseline body weight.
    - The future for GLP-1 agonists in psychiatry looks bright. At the moment, metformin can help prevent metabolic syndrome but doesn't reverse it. GLP-1 agonists may offer a solution.

(Note: Episode 158 with Rocio Salas-Whalen, an endocrinologist who focuses on weight management, delves further into the literature on GLP-1 agonists.)

One particularly notable study shows 50% of patients achieving 20% weight loss in a year on tirzepatide, which is extremely promising (Jastreboff et al., 2022).

Side effects of GLP-1 agonists

Side effects of GLP-1 antagonists include nausea, GERD, and vomiting (largely because they delay gastric emptying and the stomach feels very full). Patients need to decrease what they eat, especially at night. As most of these medications are titrated from a lower dose to a higher dose the nausea and GI effects tend to mitigate over time. GLP-1 agonists may also suppress thirst, potentially leading to dehydration. As a result, it's important to remind patients to keep drinking enough water.

Rare risks are pancreatitis and a theoretical possibility of pancreatic carcinoma based on hyperplasia. However, this is based on animal studies and has not yet been seen in humans. If the person being treated has not developed type 2 diabetes, the risk to the pancreas is much lower.

Another listed contraindication is for people with a family history of endocrine neoplasia syndrome type 2, a very rare genetic predisposition towards endocrine cancers. Most psychiatric doctors are not likely to run across many patients with that history.

LAIs During Pregnancy

A review of data on the safety profile of antipsychotics, including LAI formulations, suggests prescribing them during pregnancy is safe (Reinstein et al., 2020). In fact, women with psychotic disorders are more prone to relapse when pregnant (Taylor et al., 2018), so taking away their best defense against psychotic episodes makes them more likely to become psychotic and is not usually advisable.

Serious Mental Illness (SMI) and Homelessness

Unfortunately, every predictor of SMI can be found in the homeless. In countries such as Italy and Austria, SMI population are discharged to a supervised house/apartment where they can stay

for up to a decade. In America, on the other hand, individuals with SMI are discharged to the street.

Mental illness appears to be a significant risk factor for homelessness; 49% of older homeless adults surveyed in Minnesota reported a serious mental illness (for instance, SAMHSA, 2011), and data also suggests that 75% of chronically homeless people struggle with substance use disorder (SUD) or an SMI (Streeter, 2022). In addition to expanded access to mental healthcare for homeless individuals, there needs to be a greater focus on stable and affordable housing, as most social programs seem to be insufficient if the person does not have stable housing.

Conclusion

Long-acting injectable antipsychotics appear effective at improving adherence, are comparably well-tolerated to other formulations, and decrease all-cause mortality. Nevertheless, they are used less than their oral counterparts in most settings. There are also a number of practical considerations, particularly with regards to drug kinetics, that providers should take into account when using LAIs.

As a society, we vastly undertreat the seriously mentally ill. LAIs are a tool we should consider using more in this population to help break the vicious cycle of hospitalization, discharge (without support/supervision), decompensation, and homelessness or incarceration.

Acknowledgments:

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Long-Acting Injectables with Dr. Cummings

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Long-Acting Injectables with Dr. Cummings

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Long-Acting Injectables with Dr. Cummings

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