

**Dr Robbins FB Live**

Questions for FB Live: February 3

# NEW ABORTIVES: UBRELVY, REYVOW, RIMEGEPANT

1. **Are the new abortive medications safe to take while on heart medication?**They are in general. If people have heart risk factors then a gepant is better or Reyvow because theoretically they don’t affect the heart. However, as always, please consult with your doctor about your particular situation. Ubrelvy attaches to the CGRP receptor just like Aimovig does.
2. **Are the new abortive medications safe to take if you have a heart condition or have had a stroke?**In general yes, unless they raise the blood pressure or have some side effect that we aren’t expecting.
3. **Can Ubrelvy, Reyvow or Rimegepant help with chronic migraine or just episodic?**These medications are used for both types of migraine and do not differentiate between episodic or chronic.
4. **If someone is taking CBD or THC then is Ubrelvy contraindicated, need a dose modification, or safe to take since they are CYP inhibitors?**CBD and THC are interesting. The way we look at metabolism of drugs there are a number of ways. One is through the liver and both CBD and THC affect the CYP enzyme system which could mean you end up with higher levels of medications than is normal. Because there is such a wide range of strengths of CBD and THC it will depend on that. Also, there is a lot of disagreement about whether CBD and THC are strong or moderate CYP inhibitors, so there are a lot of unknowns. Since Ubrelvy is metabolized through the liver it has a warning in the medication guide that it is impacted by CYP inhibitors and depending on the inhibitor there may be a contraindication or a dosage modification required. With Reyvow there are multiple ways of metabolism so it is possible that CYP inhibitors won’t have so much of an impact as they will with Ubrelvy.
5. **Are the gepants safe to take with the CGRP injectables or eptinezumab?**Right now there are no contraindications, but it is possible that there will be contraindications in the future because this is another area of unknowns.
6. **Do the gepants cause rebound headaches (MOH) like the triptans can and what is the max number that can be taken per month?**Gepants did not show MOH risk in the clinical trials and so there is no official high end number of pills at this point in time. Medication Overuse Headache (MOH) is often over-diagnosed and poorly defined and is frequently confused with Medication Overuse (MO). MO does not necessarily cause MOH! The high caffeine drugs, opioids and butalbital drugs are the most likely to cause MOH and for this reason they should not be a first-line resort for migraine medication and need to be carefully monitored so that they are not overused. Diagnosing MOH requires a careful history rather than an immediate assumption that because medications are being overused they are therefore causing medication overuse headaches. Even though the situation has improved over the past few years with botox and the CGRP injectables, our preventives are still not very good, and people still tend to take too many abortives just so they can function. Again, there is no indication that the gepants will cause MOH at this point in time.
7. **How many Reyvow is it safe to take per month bearing in mind MOH and other factors?**Reyvow just came out and was given a schedule 5 labeling which means it is a mildly controlled drug. This is because some people got mildly euphoric with it. For a point of comparison, Xanax is a schedule 4 drug. Reyvow will be available in packets of 8 and is the first in its class of “ditans.” It is different than the triptans since it does not cause vasoconstriction, and so may be considered possible for high risk patients. It can only be taken once per day, not because it’s long-acting, but because in the clinical trials adding a second pill did not seem to increase the efficacy.
8. **Are we likely to see similar side effects to the gepants compared with those side effects that have been emerging in real world use of the CGRP injectables such as constipation, hair loss, fatigue, insomnia, abdominal pain, hormonal changes, etc. since they are also CGRP inhibitors?**It is unlikely that we will see similar side-effects because the gepants have short half-lives of only a few hours versus around 30 days like the injectables. Unless we start using them every day in the future it seems unlikely that they will have similar side effects. Of course, studies are only studies, so it remains to be seen what happens in real life use, and if rimegepant and atogepant are approved for preventive use then that may have different results in terms of side effects.
9. **Are there any concerns for long-term side effects at this point in time?**With any new class of medication we are very concerned about long-term side effects. CGRP is involved in many of our body systems including in the brain. For some reason evolution deemed this molecule to be very important and so blocking it long-term is unlikely to have no side-effects. However, for right now we simply don’t know.
10. **Do the gepants or Reyvow potentially cause serotonin syndrome?**Serotonin syndrome is a source of huge confusion. It can cause high blood pressure, sweating, etc. and it is a true medical emergency. Unfortunately, it got added to the PDR (Physicians Desk Reference) as a caution for several triptans and MAOIs. Subsequent studies have shown that we are not likely to get serotonin syndrome just with using one of these medications – it is extremely rare. It seems unlikely that either the gepants or Reyvow are a high risk for this even though Reyvow has a written indication for it.
11. **If the abortives don’t work with the first or second dose, is it worth taking another dose the next day?**The “next day” is usually a continuation of the same migraine, so if it worked one day it may be reasonable not to switch medication and use the same treatment(s) again.
12. **Did the clinical trials show any difference in efficacy for the new abortives between different types of migraine?**Generally, the answer is no for both the new abortives; they are used for migraine with and without aura.
13. **Did the clinical trials show any difference in efficacy between men and women?**Most of the studies included primarily women but did also have some men; we did not see any difference in efficacy between genders.
14. **Are any of these abortives safe to take with SSRI medications?**They appear for the most part to be relatively safe as seen in the clinical studies.
15. **Can any of these abortives be taken the same day as a triptan abortive or does there need to be a time gap?**You can take a triptan in the same day as a gepant, although probably not at the same time. A wise approach would be to spread them out a few hours.
16. **How is Reyvow different from the triptans?**It is very different because it theoretically does not affect the heart or cause vasoconstriction and so is not a risk for stroke or other cardiovascular conditions.
17. **If one of the CGRP injectables did nothing, increased migraine, or caused bad side effects, is it worth trying the gepants?**It is probably somewhat apples and oranges to compare the two classes because the gepants have a short half-life and are generally not used every day. The side effect profile from the injectables is likely to be different than that seen with the gepants. However, we will see for sure over time whether there is any correlation.
18. **If the preventive injectables work well for me then is it more likely that the gepant abortives will work and vice versa?**
There is not necessarily any correlation about this right now. Again, we will see for sure over time.
19. **Can you explain why Reyvow went through DEA scheduling and what the ramifications of that may be?**Reyvow went through a DEA review because in the clinical trials it caused a slightly euphoric reaction in some people. As a result, it was given a schedule 5 classification which means It is a mildly controlled substance. That may make it slightly more difficult to access than if it were not scheduled, and some doctors are more cautious about prescribing scheduled medications. However, it is the lowest classification for a scheduled drug so hopefully it won’t change too much.
20. **Do you know about any plans for these new medications in Europe, Canada and elsewhere?**Ubrelvy is not under consideration in Europe and Canada as far as we know. There is something about Reyvow in Europe, but we do not know the details yet. The monoclonal antibodies are already in many countries, but often these medications come out in the USA first and depending on the country it can take a while for new meds to be released.
21. **Are there going to be further studies with Ubrelvy, Reyvow and Rimegepant on patients with heart conditions, chronic pain conditions, and minors?**These medications will likely be used with patients who have heart conditions. Probably there will be post-approval studies of some kind, as well as in adolescents and others under 18.
22. **Are these medications safe to use on adolescents?**There is a lot of CGRP in our brain and hormonal areas and while there is little penetration of the large molecule CGRP injectables into the brain there is still a small amount. Two areas of concern are part of the hypothalamus and the posterior pituitary, both of which have a lot going on and a lot of hormones. These medications may influence what is going on there and so there should be a lot of caution about using these medications with adolescents until we know more from safety studies. Right now, there are no studies on any of the new abortives with adolescents and so caution is also necessary with them.
23. **How are side effects determined and then updated?**
There are several reasons why side effects seen in studies are often different than those seen in real life and a couple of years later the medication inserts are subsequently changed:
**FIRST**, the studies are not powered for side effects. They are not done for a long enough period of time and there is no checklist given to participants for side effects. People are simply asked if they are having any side effects in general (“How are you doing on the medication?” – this is often answered with “no, not really.” If we use a checklist study then the result is often very different. We have just finished writing up a checklist study and we will make that available as soon as it is finished. It’s very interesting.
**SECOND**, there is often disaggregation of side effects terms during clinical studies. For example, “fatigue” could be named several different things such as tiredness, somnolence, fatigue, etc. and each once could be given a low percentage which is then dismissed, whereas if similar terms were actually aggregated it would be more accurate. The FDA mandates how side effects are acquired, so you couldn’t do a study for long enough with enough patients to make a study powered for side effects. We have a hard enough time getting enough patients to do the current studies.
**THIRD**, patients in studies tend to be “cherry picked” and are often milder than seen in real life.

[QuarterWatch](https://www.ismp.org/quarterwatch) is a great organization that reviews different medications and they reviewed the monoclonals in August 2019. You need to register to have access to their reports, but registration is free. In order to evaluate post-approval side effects we need post-approval studies, doctors’ comments, reports made by patients and doctors on the FDA website, and reports made to the pharmaceutical companies. Side effects made to the FDA are shown on the [FAERS public dashboard website](https://www.fda.gov/drugs/questions-and-answers-fdas-adverse-event-reporting-system-faers/fda-adverse-event-reporting-system-faers-public-dashboard) which is updated every quarter and we are currently waiting for the December 2019 update, but as of September there were over 22,000 side effects reported. It can get really tricky working through the reports and figuring out which symptoms were actually caused by the medications and which were not. We certainly seem to be getting a more realistic picture now than a year ago, so that is good.
24. **Is it ok to take an anti-emetic with Ubrelvy, Reyvow or Rimegepant?**Many patients take ondansentron (Zofran) and ginger (available in capsules if preferable) for nausea. There are also some older ones such as promethazine, metoclopramide and compazine. They appear to be safe to take with these new abortive drugs.
25. **If one of these abortives doesn’t work, is it safe to take a rescue medication the same day such as ketorolac?**A lot of the serious side effects seen by doctors appear to be from the strong anti-inflammatories and so while they are very useful we don’t want to overuse them. They affect the stomach and kidneys. These include aleve, ibuprofen, advil and the stronger ones such as ketorolac. They are not addictive and tend not to cause tiredness, but as you get older these have a higher risk. Right now, there is no data on using rescue medications together with the new medications, but currently it appears to be safe to take an NSAID at the same time as Ubrelvy.
26. **Can we take a triptan at the same time as Ubrelvy?**It may not be wise to take a triptan at the same time as Ubrelvy but we don’t have any data on this. A recommendation for right now would be to space them out by a few hours (2-4 hours). They can be used on the same day but probably not at the same time until we know more.
27. **Can you take the preventive medication topiramate and Ubrelvy together?**Topiramate in higher doses (over 100mg) is a CYP inducer so it may decrease the levels of Ubrelvy. For example, 100mg of Ubrelvy may actually appear like the 50mg dose.
28. **If someone has severe migraine can these new abortives be used if they wake up with a bad attack?**
You can use these new abortive medications at any time, but generally with migraine the sooner an abortive is used in the attack the more effective it will be.
29. **Can Ubrelvy or Reyvow be taken if you have hemiplegic migraine?**Right now, there is no contraindication for Ubrelvy, and Reyvow theoretically should be ok also because neither increase the risk for stroke as far as we are aware. Bear in mind that both medications JUST came out, so we don’t know for sure and it will remain to be seen in real world use.
30. **Do we have any updates on rimegepant or other gepants?**Right now, we do not know the approval date for this although the company indicated it should be sometime in the first quarter of 2020. They are also working on a preventive indication on top of the abortive indication, but that is likely to get FDA approval later. There is also a daily preventive gepant expected to apply for FDA approval by the end of this year called atogepant, and a nasal spray abortive called vacegepant that is in stage 2/3 clinical trials.
31. **How long will it be before MediCare covers these new medications?**
Generally, it takes a while for new medications to be covered by MediCare part D, however there are three different ways to have MediCare (straight MediCare with part D, MediCare plus Supplemental, and MediCare Advantage) and both the supplemental and advantage versions come with a wide variety of different options. Straight MediCare part D may take longer to approve the new medications, but we are already seeing some Advantage Plans approving Ubrelvy as a “non-formulary exception.” The challenge is that for some plans the new medications may be put into a higher “tier” of medication and so the copays may make them inaccessible.

Part of the problem with MediCare is that there is a myth that people in their 50s or over 65 no longer get migraine attacks. In reality, there is a 45% chance that your migraine attacks will get much better or even go away. However, some people start getting headaches in their 50s and 60s. There is some evidence of NDPH in the 75-85 age range. Because of this myth, there are few studies done on the “elderly.” We need more evidence on medication use in the 65-75 and also in the 85-100 age range. In the meantime, it is a problem.

# EPTINEZUMAB

1. **What can you tell us about the new monoclonal antibody expected to be FDA approved in February 2020?** Eptinezumab is an intravenous medication given in a doctor’s office every three months and takes 20-30 minutes for the IV. We are still trying to parse out the differences between the monoclonal antibodies.
2. **Does eptinezumab work faster than the current three injectables?**It appears to work faster than the other monoclonal antibodies and there are higher blood levels with it.
3. **What is the half-life of eptinezumab?**The half-life is 27-31 days similar to the other monoclonal antibodies.

# CGRP INJECTABLE UPDATE

1. **Are there any new updates on recognized side effects from the CGRP injectables such as hair loss, fatigue, abdominal pain, insomnia, hormone changes, impact on abortives, change in efficacy after taking for a while?**The main side effects that we are talking about for the monoclonal antibodies are tiredness, joint pain, hair loss or thinning, depression, anxiety, insomnia and other annoying side effects as well as some serious side effects. A certain percentage of patients appear not to be able to take these medications because of side effects and unfortunately once you take the injection it is long-acting and so the side effects can sometimes be long-acting. We expect that the package inserts will be greatly changed as we work through the reports.

There are two types of side effects the FDA looks at. There are ones that are annoying and sometimes people will put up with these if the medication works. Others are too annoying to be tolerated. Then there are ones that are serious and could result in hospitalization or even death. A lot of people will put up with annoying side effects when they find something that works, but if side effects continue or are too severe then it’s often not worth it.
2. **How long do the side effects of the injectables last?**
For most people they wear off within a month or two, but for some people they last longer. They all have a long half-life (27-30 days) and generally it takes five half-lives for a medication to be completely out of your system. That’s around five months with these medications. For those with a fragile nervous system or fragile brain the side effects can last a long time or potentially cause long-term change.
3. **Do the monoclonal antibodies cause high blood pressure?**
CGRP is involved in blood pressure and so inhibiting it can potentially impact that. We haven’t seen a lot of people with this side effect, but we are definitely seeing it. The question would be whether to stay on the medication in this situation. There may be a risk-benefit to staying on it even if you have to then treat the high blood pressure with an additional medication, but that will be an individual determination to be figured out with the patient and doctor. In general we don’t like treating the side effects of one drug with another drug, but sometimes it is beneficial to take that approach.
4. **Why do the injectables seem to “wear off” for some people and is it worthwhile switching when this happens?**
The injectables do seem to have a wear off effect for some people. If you have a lack of efficacy or the medication wears off, then switching only seems to result in a 25-27% success, although bear in mind that for that 25-27% it’s good. If people switch due to side effects then there is closer to a 30% success rate. For people who have to switch because of finances, or their insurance no longer pay for the one they’re on, we have about a 58% success rate. In general, it is worth switching injectables and seeing if a different one works and is tolerable.
5. **Can you get new side effects after being on the monoclonal antibodies for a while?**Generally, it appears as though most of the side effects to these medications start to appear within the first month or two. We don’t usually see people doing well and then suddenly getting side effects after four months. It can happen but it’s not that common.
6. **Are the monoclonal injectables actually helping people?**
They are definitely helping some people who were not helped by anything else, and in many people have transformed lives. We needed better tools in our toolkit, and it is great that we now have expanded choices.

# ADDITIONAL LIVE QUESTIONS

1. **How do we decide which medication to try for migraine?**We have to look at a wide range of factors for that and it is individual for each person.
2. **Will these new medications help with cluster headaches?**They have not been tested for cluster headaches yet and so we don’t know at this point in time. There is a great need for new medications for cluster headaches.

**NEW QUESTIONS:**

1. Is it safe to take both Ubrelvy and Reyvow together or in the same day? Yes, probably(until we know otherwise)
2. When will the new abortives be available as injections or nasal sprays so that they work faster and bypass the GI system? Probably will not come out that way
3. Can CGRP injections be used for daily headaches due to post concussion syndrome? Yes, several studies have been done, but they probably work better if there are migraine components to the daily headaches.