Paroxetine, septal defects, and research defects

Many years ago I was asked to consult a drug company on a possible causal connection between taking some drug and a devastating disease. I believe the case never made it to court but I got a chance to think not only about methodology, but also about the fascinating topic of how the layperson, and probably judges too, think about causality.

More recently, by way of inquiry, I learned about another drug-related causal question that might end up in court, if it hasn't already: the possible effect of taking Paroxetine in the first trimester of pregnancy on congenital atrial septal defect (ASD), congenital ventricular septal defect (VSD), or both.

Before discussing the topic any further, let me show you how different wording could have set a different tone to the previous paragraph.

Instead of writing "the possible effect", I could have written "the possible adverse effect", or "the possible teratogenic effect". I could also have replaced congenital ASD and congenital VSD with "congenital cardiac malformation", or "congenital heart defects". And you can probably come up with similar alternative phrases, all of which create a sense of alarm before sharing any piece of data.

Wording aside, it is common to hold some prejudice against drug companies because many of us like to dislike money making giants. As you might know, however, most medications have been discovered by the pharmaceutical industry rather than by taxpayer money. So let's not ignore the mundane causal connection between the desire of a business to make money and the desirable outcome for others.

Platitudes first

All drugs have "side effects" – undesired effects that are not always "on the side". When someone takes Coumadin to prevent embolic stroke and bleeds into the brain, that's a major effect, not a side effect. You may call it "a major side effect", but that's a rhetorical twist, if not a silly contradiction.

Paroxetine, a member of the SSRI class, is a pharmacological agent, not a natural nutrient that healthy people gladly ingest. When the drug is prescribed to a pregnant woman, someone thought that the lady needed it badly. Depression and anxiety, for which Paroxetine or some other drug is given, are serious conditions – not only because the person suffers tremendously, but also because depression can lead to attempted suicide, which might be successful. I will never forget a dear friend – she neither was pregnant nor took Paroxetine – who ran in front of a bus because she could not tolerate anymore the darkness in which she had been living. (That's how she used to describe her depression.) Depression is a devastating condition, and so is anxiety disorder.[a]

No doubt that the baby's wellbeing is of utmost importance, but the wellbeing of the baby's mother is not less important. And let's not forget that the causal path "depression→suicide" endangers the baby, too. Suppose taking Paroxetine has two effects: increasing the baby's chance of having congenital septal defects and reducing the baby's chance of dying in uterus (by reducing the chance of maternal suicide). How do we weigh the two effects to decide on taking Paroxetine? We can't ask the baby about its preference, but an adult would prefer to be alive with ASD than dead (without).

There are other antidepressants – you may argue – that alleviate depression and reduce the chance of suicide without increasing the chance of congenital septal defect. Well, you have just argued that relevant research should compare pregnant women who took Paroxetine to pregnant women who took a different antidepressant – *not to pregnant women who did not take any antidepressant*. I agree. Let's ignore any study that included in the comparison group ("unexposed") depression-free women or depressed women who did not take any antidepressant because it is not answering the relevant question. In fact, there is another good reason to restrict the sample to women with depression. It is called bias.

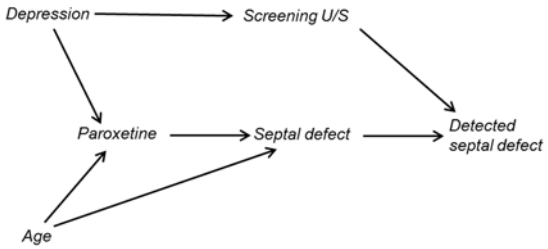
Confounding bias and information bias

Most researchers like to explain bias in words. I prefer causal diagrams, a clear and simple method to depict any type of bias (and name it correctly).[1] Though never complete, a causal diagram serves us well as long as it shows enough details to make a point.

[a] To simplify, from now on I discuss only depression. Most arguments hold for anxiety disorder, too, and sometimes both disorders coexist.

Figure 1 shows two threats of bias in studies of Paroxetine and septal defects: confounding and information bias.

Figure 1.



A confounder is a shared cause of the exposure and the disease – age, for instance. If age is a cause of Paroxetine use (say, prescribing behavior is influenced by the woman's age) and maternal age affects septal defects, then part of the marginal association between Paroxetine and septal defects arises from the open path "Paroxetine←Age→Septal defect" (Figure 1).

Although most researchers know what confounding bias means, many of them don't know that we often pay a price to remove it: increased variance. So keep the following in mind before declaring that your estimate is good "because potential confounding by A, B, C,…,X, Y, and Z was removed by multivariable logistic regression". Your adjusted estimate has now come from a distribution with a larger variance,[2] and the chances of being close to the truth (the center) have been reduced. "Adjusting for everything but the kitchen sink" – a phrase I have once heard – let the sink remain (no big deal indeed), but might also allow a noisy estimator to take over the kitchen. At most, studies of Paroxetine and septal defects should adjust only for presumed causes of septal defects, and preferably only to known causes of *both* Paroxetine use and septal defects. The list of such variables is fairly short.

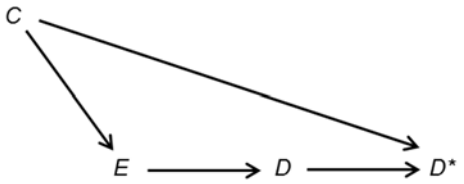
Depression is a cause of taking Paroxetine, but it is not a known cause of septal defects. Therefore, it is not an *a priori* confounder.[b] What problem does it create, then?

Figure 1 shows the problem. Women with depression are more likely to undergo ultrasound screening during pregnancy, and their babies are more likely to undergo screening after they are born – a plausible theory that was substantiated empirically.[3] Since screening increases the chances of detecting septal defects, and the variable we analyze is "detected septal defect", we observe an open path that contributes to the marginal association between Paroxetine use and detected septal defect (Figure 1):

Paroxetine←Depression→Screening→Detection

That's a path of information bias.[c] In historical writing the phenomenon was labeled detection bias. In contemporary writing the structure of the bias fits a generic diagram $E \leftarrow C \rightarrow D^*$ (Figure 2). A cause (C) of the exposure (E) is also a cause of *measured* disease (D^*), not through D.

Figure 2.



How do we block this path? How do we eliminate this source of bias?

"Adjustment" for depression status does not work. To adjust for a binary variable, through stratification or regression, requires pulling two stratum-specific estimates (e.g., depression=yes, depression=no) of the effect of interest. But we cannot estimate the effect of Paroxetine in the absence of depression. There are no users of Paroxetine in this stratum. Depression-free, pregnant women do not take the drug.

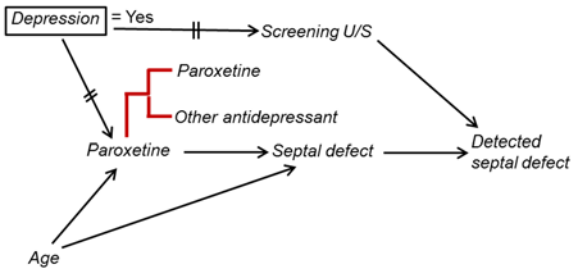
To block the path and remove information bias, *we must restrict the study sample to pregnant woman who suffered from depression*. That should solve the

[b] There is a subtle issue here, which I discussed in another commentary here (Insight on confounders). If Paroxetine has a non-null effect on septal defects, any cause of Paroxetine use is a confounder even if it affects septal defects only through Paroxetine use.

[c] Some authors mistakenly call it "confounding by indication". First, a confounder is a cause of the disease, not a cause of detected (measured) disease. Second, "confounding by indication" is a superfluous phrase. If D (disease) is the indication for prescribing drug E, then D is a cause of prescribing E ($D \rightarrow E$). And if D is a confounder for the effect of E on some outcome, Z, then D is also a cause of Z ($D \rightarrow Z$). "Confounding by indication" neither differs from any confounding nor deserves a special label. It is not more worrisome than confounding by any other variable, and it is not worrisome at all if the effect of D on Z is close to null. A confounding path ($E \leftarrow D \rightarrow Z$) that contains a very weak link ($D \rightarrow Z$) does not contribute much to the marginal association between E and Z.

problem of information bias (Figure 2). And if we compare Paroxetine users (exposed) to users of a different antidepressant (unexposed) – not to untreated women – we will also address the relevant causal question, as was explained in the previous section (Figure 3).

Figure 3.



If the ideal design (Figure 3) is not common, we should be looking for studies or analyses in the following order of relevance to the effect of Paroxetine on VSD and ASD (least relevant to most relevant):

1) Restricted to women with depression. (At a minimum, the path of information bias was eliminated.)

2) Restricted to women with depression who were treated with any SSRI versus other antidepressant. (Belonging to a class does not imply that all members of the class share the same effect on every possible outcome.)

3) Restricted to women with depression who were treated with Paroxetine versus other SSRI, or versus other antidepressant. (The ideal design.)

The list above should be considered in conjunction with the following order of relevance to the outcome (least relevant to most relevant).

1) Any cardiac malformation
2) VSD or ASD (combined)
3) VSD or ASD (separately)

For example, a study of any cardiac malformation in babies of women with depression who were treated with any SSRI versus women who were not treated is least relevant. It is several steps removed from estimating the effect of Paroxetine on ASD (or on VSD). Conversely, a study of ASD in babies of women with depression who were treated with Paroxetine versus other antidepressants is most relevant. Again, studies or analyses that included depression-free women have no merit twice over: 1) They embed information bias; 2) They address an irrelevant causal question.

A taste of the literature

The broad topic of Paroxetine and congenital heart defects was addressed by over 20 studies and at least four meta-analyses. Each publication deserves a careful review in light of the premises I presented here. For now, I will sample only one recent meta-analysis[4] and offer a limited set of comments rather than a thorough critique.

The principal findings are stated in the abstract:

"Twenty-three studies were included. Compared with non-exposure to paroxetine, first trimester use of paroxetine was associated with an increased risk of any major congenital malformations combined (pooled OR 1.23, 95% CI 1.10, 1.38; n = 15 studies), major cardiac malformations (pooled OR 1.28, 95% CI 1.11, 1.47; n = 18 studies), specifically bulbus cordis anomalies and anomalies of cardiac septal closure (pooled OR 1.42, 95% CI 1.07, 1.89; n = 8 studies), atrial septal defects (pooled OR 2.38, 95% CI 1.14, 4.97; n = 4 studies) and right ventricular outflow track defect (pooled OR 2.29, 95% CI 1.06, 4.93; n = 4 studies)."[4]

Ordered by outcome relevance (least to most), we have three odds ratio estimates:
1.23 (n=15 studies)
1.42 (n=8 studies)
2.38 (n=4 studies).

A nice trend of strengthening, accompanied by a less appealing trend of halving the sample size (with no relevant comment in the abstract).

Reviewing previous work, the authors write:

"However, some relevant studies were not included in Myles et al. [40], and the majority of studies used did not distinguish between the potential effect of depression (the underlying condition) and the drug (paroxetine) on the risk of major and cardiac malformations."

Apparently, the authors intuitively understood that depression status must play a key role, but they stop short of explaining what "potential effect of depression" they have in mind. Nonetheless, their writing about distinguishing the effect of depression

from that of Paroxetine is the typical language for confounding bias. If that's what they had in mind, they are wrong. As shown in Figure 1, the bias in question is information bias, not confounding bias. Depression is not a cause of cardiac malformation and therefore it is not a confounder; it is a cause of *detecting* cardiac malformation – a source of information bias (Figure 1).

They continue:

"There is a strong recommendation for studies to include untreated patients with depression and/or other psychiatric diagnoses [41]. Recent studies have attempted to overcome this by including a comparison group of untreated depressed patients [16, 42–44], some of which were not considered in previous meta-analyses."

Recommendations are helpful in many walks of life, but they are a weak argument in scientific methodology. It should be clear now why including a comparison group of untreated depressed women is a mistake. Notice that the authors don't specify the exact role of depression status, or of treatment status, in this field of research.

That they have no sharp understanding of the role of either is also evident from the next statement:

"…we aimed to conduct a meta-analysis incorporating more recent findings, stratifying on types of comparison groups to update current understanding of paroxetine and major congenital malformations…"

When you understand right from wrong (or at least claim to understand), you don't stratify a sample that contains right and wrong. You delete what's wrong and explain why it is wrong. That's especially true in a meta-analysis where researchers make upfront decisions about studies that should be included and studies that should be excluded. For instance, I explained earlier why a study that used a comparison group of untreated, depression-free women should be excluded. To sum up, we don't update any understanding by incorporating studies with a faulty design into a meta-analysis.

Lastly, here is a key paragraph in the discussion:

"The risk of any major malformations or cardiac malformations differs according to the comparison group used. In our meta-analysis, the highest risk estimates were obtained when the comparator included women exposed to a non-paroxetine antidepressant, hence women who might be treated with other SSRIs or other antidepressants. These studies are therefore adjusting for the indication per design. The most used comparison group included women unexposed to any antidepressant. Although choice of comparator group varied the risk estimate, it remains that there was a general trend towards increase in risk."

Let me decode the paragraph for you:

First, "a comparator" that includes women who took anti-depressants means "women with depression". But including women with depression is not synonymous with *restriction* to women with depression…

Second, "adjusting for indication per design" actually means "blocking the path of information bias". Again, they continue to view the role of depression as "confounding by indication" (false) and use the term adjustment where no adjustment is possible. It is only possible to condition on Depression=yes, as explained earlier. That's called restriction, not adjustment.

Third, when you adjust for a variable ("condition on" is a better phrase), you should always have some expectation (theory) of the expected results. Here, we do *not* expect that "adjusting for indication per design", which actually means "blocking the path of information bias due to depression", would *strengthen* the association ("highest risk [ratio] estimates"). On the contrary, we expect exactly the opposite: smaller risk ratio estimates! What theory explains these unexpected results?

Fourth, "The most used comparison group included women unexposed to any antidepressant" tells us that the most commonly used design was faulty…

To be continued….

References:

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