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Why are epilepsy trials failing? Interview with Emilio Perucca

"...we need to change the current situation and the way governments and multinational agencies support research for epilepsy and specifically the funding for clinical trials."

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Q You recently attended the antiepileptic drug trials XI meeting in Florida, what would you say were the most important points of debate?

Well, I think the most important issues raised were to do with the difficulty in assessing outcomes in antiepileptic drug (AED) trials. AED trials are increasingly failing, so we discussed the possible causes for such failures and the options to improve trial designs and to address current recruitment difficulties.

Q New concerns over the risk of suicidality in epilepsy trials were raised at the meeting, what would you say were the most important points of debate on this topic?

As you will know, this is a controversial issue. The whole thing started when the US FDA analyzed data from past adjunctive-therapy AED trials and showed an increased risk of suicidal ideation and suicide in people randomized to AEDs compared with those randomized to placebo. There have been a number of criticisms in the way this analysis was conducted, one point in question being that these drugs work by different mechanisms and have different side effects, and it is questionable to lump them together as a single class. When you in fact look at individual drugs, the signal (of potential risk) is there for many drugs, but it is not there for all drugs and moreover, in additional studies the results have not been fully consistent. So the concern of the epilepsy community is that we may produce undue alarm among physicians and people with epilepsy, and that that alarm could actually lead to people potentially discontinuing treatment, which would have much (more) serious consequences than those we are discussing now. These concerns were reiterated at the meeting.

Although it appears that some epilepsy drugs do carry an increased risk of depression and suicidal ideation, the actual risk of this leading to suicide is relatively small. It should be realized that in most people with epilepsy the benefit of taking these drugs is far greater than the associated risks. However, as the risks exist, physicians should be aware that they need to monitor a patient for depression and for suicidal ideation, and they should take action if such changes in clinical state emerge. One part of the meeting was devoted to discussion of how such monitoring could take place. A number of screening processes were suggested and the recommendation was made that patients who turn out to be positive should definitely be referred to psychiatric evaluation.

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Q By 'positive' do you mean patients who display signs of depression in the screening process?

I mean positive for a degree of depressive symptoms which could indicate a significant risk of suicide. So there is scope for screening for people who are at risk of developing suicidal ideation, or who do develop suicidal ideation which needs somehow to be managed. The FDA now requires that patients in clinical trials are monitored for this.

Q What was the consensus of opinion at the meeting on this proposed screening and handling procedure?

The consensus was that it is sensible to implement such monitoring and that we (the epilepsy community) should continue to address this concern. However, it was reiterated that this risk (of suicidality) is probably over emphasized and that we need to put it in perspective. It may be incorrect to assume that the risk is there for all drugs and we need to acknowledge that there may be differences between drugs with respect to this risk.

Q One of the most pressing issues at the moment relating to AED trials is the lack of agreement between US and European regulators on a monotherapy trial design for licensing a drug for the treatment of newly diagnosed epilepsy. What impact would you say this lack of consensus is having on epilepsy research and the path to development?

The consequences are clear. Companies that wish to license a drug for monotherapy in Europe and the USA have to do two different kinds of studies: studies that are done to satisfy the European Medicines Agency requirements and studies that are done to satisfy the FDA requirements. Studies needed to address the European Medicines Agency requirements are well qualified in the guidelines published in 2000 [101] and in 2010 [102]. The 2010 guidelines basically reiterate that the investigational agent should be evaluated at optimized dosages in a long-term trial in people with newly diagnosed epilepsy (the primary population that the investigational drug is intended to treat), using as a comparator the 'gold standard' reference treatment for that indication, also at optimal dosages.

While European authorities would not object to such a trial having a superiority design, in practice it is usually unrealistic to expect that the investigational agent will be more efficacious than the current 'gold standard' in this setting. Therefore, the most realistic option for a company wishing to obtain a license for a new drug is to conduct a non-inferiority study. According to European Medicines Agency guidelines, such studies need to have 6-month seizure freedom as a primary end point and a further follow-up of at least 6 months to make sure that seizure control is maintained. This is the paradigm used in Europe: basically, non-inferiority studies versus an active comparator with seizure freedom as a primary end point and a follow up of at least 1 year. In practice these studies require a longer duration because it takes time to recruit patients and to optimize dosage.

Q And in the USA?

In the USA, the FDA argues that the paradigm that the Europeans have come up with lacks assay sensitivity. In other words, there is no evidence that a design such as the one used in Europe, would consistently differentiate an active compound from placebo or a less effective treatment, if this was given. Because of this, it is possible that under the conditions in which such a (EU-required) study is conducted, the two treatments, if non-inferiority criteria are met, could be equally ineffective, instead of being equally effective. Basically, the FDA is not querying that the comparator is efficacious, what they query is whether, under the actual conditions in which the study was done, the comparator would have shown a difference – superiority – over an inferior treatment or placebo.

This is the FDA argument, which is understandable. Because of this, studies done to obtain a monotherapy license in the USA need to show superiority of the investigational agent over a comparator. The design most commonly used to address FDA requirements has been the so-called conversion to monotherapy design. In this design, AED-treated patients who still have seizures are randomized to be switched from their current treatment to monotherapy with either the investigational drug used at a high dosage or an active comparator used at suboptimal doses – the latter could be a lower dose of the same drug which is being tested. A number of exit criteria are then chosen to protect patients in the study if their seizure control deteriorates. Proof of efficacy of the investigational agent is obtained by showing that the exit rate in the high-dose group of the investigational treatment is lower than that in the group assigned to suboptimal treatment. So, basically, the design used in the USA is a design by which the effectiveness of a drug is documented by showing that people randomized to that drug deteriorate less compared with those randomized to a suboptimal treatment.

Q This must raise some ethical concerns?

Yes, ethically we are concerned with randomizing people to a monotherapy with something which is known to be suboptimal. Apart from these ethical concerns, another issue is that we are approving a drug by showing that it does not cause as much deterioration as a suboptimal comparator. This is not ideal: you would like to approve a drug showing improvement, not showing less deterioration. Lastly, the high doses of the investigational agent which are tested in these trials are likely to be far greater (and to cause more toxicity) than those required to control seizures in people with newly diagnosed epilepsy.

The ethical concerns have now been partly addressed by the fact that the FDA performed an analysis of all such studies conducted so far and found that exit rates in the groups randomized to suboptimal treatments have been remarkably consistent across trials. This led to establish a set of historical controls with which an investigational agent can now be compared. So now (in the current approach) patients no longer need to be randomized to a suboptimal treatment arm. They can be randomized to a full dose of the investigational agent and another full-dose active control – you still require two arms to reproduce the same experimental conditions as in the previous studies. To obtain FDA approval, the investigational agent needs to beat, according to well-defined criteria and confidence limits, the outcomes observed in historical controls.

Q Surely reproducing historical controls raises its own problems in terms of recruitment and the relevance of the results?

There was considerable discussion in Miami about a study which was done with lamotrigine XR [103]. This was the first study done with the historical control design, for which results were submitted to the FDA and presented at the meeting. The problem is that it is very difficult in 2011 to carry out a study in a population which is absolutely similar to the populations in which the historical controls were evaluated. In particular, patients these days are receiving background treatments which are different from those they received in the past, so really we are dealing with populations for that comparability is a concern. I think in the case of lamotrigine XR the FDA has done a superb job in looking for loopholes and doing a lot of subanalysis, for example looking at outcomes in subgroups with different underlying medications and other characteristics. Overall they found that outcomes associated with lamotrigine XR remained consistent in the different subgroups. Still, there is some sense of unease in the community that this kind of artificial set up is not providing the kind of comparison that we would like to have and that we should still look at ways to improve study designs.

One point that was raised (at the meeting) was that in other therapeutic areas a drug tested in patients receiving co-medications may also be approved for monotherapy use without the need for separate monotherapy studies. It is only in epilepsy and a few other areas, that separate studies are required to obtain the monotherapy indication. In fact, there is no evidence that if an AED works as add-on therapy it would not also work as monotherapy. I suspect this is something that we will be discussing more and more in the future with regulatory agencies, and see whether eventually we might not be able to eliminate this dichotomy of having to perform separate studies (adjunctive therapy and monotherapy) and not just simply allow monotherapy approval irrespective of the co-medications. Once you have shown efficacy, of course you will also need to take into account the effect of drug interactions, but basically many of us think that current monotherapy designs do not adequately address the clinical needs.

Q In the interim, before an improved design is implemented, what is your opinion on the best approach in the current environment?

Indeed, for the time being we have to live with the current situation. In my opinion, this has disadvantages but also one advantage. The US approach provides scientifically undisputable evidence that a drug works using a design that is somewhat artificial and difficult to extrapolate to the newly diagnosed epilepsy setting. On the other hand, the design used in Europe is less sound from an assay-sensitivity point of view, but it does compare drugs as they are used in real life and in a way that is more meaningful for physicians. So, what is happening now is that when there is a drug approved in Europe and in America, we have two sets of information that are somewhat complementary.

Q As a physician, which dataset do you find most useful?

Personally I feel more comfortable with the European dataset because it is obtained in a setting that reproduces everyday clinical practice. The design used in the USA is more artificial and gives little comparative data of relevance to everyday practice. In fact, the conversion to monotherapy design with historical controls tells you that a drug is better than nothing (or better than a poorly active treatment), but it tells you nothing on how that agent compares with existing medications, or what dosages are likely to produce the best response.

Q So at the moment, using both criteria, drugs wanting approval need completely different studies, placing a financial and administrative burden on pharmaceutical companies. Do you think this hinders drug development?

Yes, there is no doubt this is correct. The current situation is a disincentive to invest into epilepsy because the bar that needs to be passed for monotherapy approval is very high. In fact, data presented in Miami showed that meeting the non-inferiority end points in the study design used in Europe is not as easy as some people may think. In a study that compared pregabalin with lamotrigine, lamotrigine being the active comparator [1], pregabalin failed to meet the non-inferiority criteria. Pregabalin was actually inferior to lamotrigine. So, the sponsor spent a significant amount of money to perform a study that did not deliver what they needed.

These studies, particularly those using the European design, are very expensive. The pregabalin study is actually a good example. Because of the concerns we are discussing, often companies try to minimize study duration by hoping that the majority of patients would respond to the initially chosen dosage. In the pregabalin trial, the final results were indeed largely determined by the choice of the initial dose, which was probably too low for pregabalin, and the study failed because the protocol did not allow for sufficient time to optimize dosage. The outcome of that study might have been different with a protocol providing better opportunities for dose optimization, but this would have prolonged the study by at least 1 year and would have increased costs substantially.

Q Moving on, what would you say is the impact of globalization on epilepsy trials?

There are two issues here. One is that it is increasingly difficult to recruit patients into placebo-controlled studies in Europe and the USA. Here I am not discussing monotherapy trials. I am referring to the adjunctive therapy placebo-controlled design, which we have been using in substantially unchanged form for more than 20 years. In this design, patients who did not respond to available therapies are randomized to receive add-on treatment with the investigational agent or placebo. In the past, these studies were easy to do, now they are not. Unlike the situation in the past, there are now more than 15 drugs to treat epilepsy in Europe and the USA. It becomes ethically difficult to ask a patient to try a placebo or something new when there still may be seven, eight or nine established drugs that that the same patient has not tried yet.

Another concern stems from a still-unpublished meta-analysis conducted by Philippe Ryvlin and his group in Lyon. This meta-analysis found that in adjunctive-therapy trials of AEDs mortality rates due to sudden unexpected death in epilepsy (SUDEP), a cause of death probably related to seizures, are higher for patients randomized to placebo than for those randomized to efficacious doses of active treatment. So, not only is it difficult to enter patients into these studies when they have other treatment options, but now we also know that we are exposing the placebo groups not just to lack of improvement in seizure control but also probably to a higher risk of mortality. This is a great concern!

In less-developed countries where there may only be three or four AEDs available, or where perhaps only one or two AEDs are affordable by low-income patients, it is much easier to recruit. That is why we have been seeing a lot more of these trials moving to Latin America or Asia, in particular. One question, however, is to what extent the population recruited in these regions is representative of the population of patients we see in Europe and the USA where the drugs in question will eventually be mostly used.

Q You have spoken about concerns regarding the placebo effect observed in these regions?

Yes, many of the studies done in this new global trial environment failed to differentiate investigational drugs from placebo. One of the reasons for this appears to be an increasingly large placebo-associated 'response'. In other words, groups randomized to placebo seem to have a greater improvement in their seizures than they used to have in the past. I presented some data that suggested, though they do not prove, that placebo responses tend to be higher in some developing countries than in Europe and North America.

Bernd Schmidt and Jackie French also presented data that go in the same direction. Perhaps the most striking example is a recent and yet unpublished study with perampanel, which recruited patients in North America and in Latin America, in about equal proportions. The drug differentiated extremely well from placebo in the North American population but it did not differentiate from placebo in the Latin American population. When the two populations were pooled, the drug only did better than placebo by a modest margin. When the two populations were assessed separately, the superiority to placebo was clear-cut in the North American cohort and virtually non-existent in the Latin American one. The latter showed a much greater placebo response than its North American counterpart.

There has been a lot of discussion on this, also fuelled by studies using drugs known to be efficacious. In one

trial in Asia, for example, levetiracetam unexpectedly could not be differentiated from placebo [2]. Again, that study was characterized by an unusually large placebo response.

Q What potential explanations have been put forward for this?

Well, the most likely explanation, based on discussions held in Miami, has not to do with a specific country or a specific ethnic group, and perhaps not even with globalization as such. Some of the examples cited above may reflect simply a trend to involve an increasingly large number of centers in clinical trials some of which are likely to be less experienced in epilepsy research. Physicians not specifically focused on (or expert in) epilepsy have also been increasingly asked to take part in these studies. When you move away from centers that are very experienced, you may end up with confounders of all sorts. These may include diagnostic inaccuracies, and less accurate monitoring of seizure counts. For example, patients in some centers may not be used to recording seizures accurately in seizure diaries as they do in most specialized centers. The issues here are complex, but the consensus that emerged in Miami was that the increasing difficulty of differentiating active treatments from placebo has to do more with heterogeneity across centers and investigators than with specificities associated with a particular region or country. Indeed, there are excellent centers in Asia and Latin America that can provide top-quality research, even better than in some centers in Europe or the USA. However, when you go to maybe 150 sites to recruit for a trial and CROs are under pressure to do the study faster, then you tend to go to centers that are inexperienced, and despite the monitoring and so on, the quality of the work, recruitment, assessment and diagnosis may not be what you require for a trial to be successful. Of note is the fact that the situation does not appear to be specific for epilepsy. I presented a meta-analysis of work done in depression showing that the placebo response is positively correlated with the number of sites in a trial, and that the ability to differentiate active treatment from placebo decreases with number of sites.

Q Does this not represent a catch-22 situation?

Yes, we are witnessing a vicious circle here. The smaller the effect size gets, the more we need to enlarge the study population and to enlist an increasing number of centers. However, the more centers we recruit, the more we lose our ability to discriminate from placebo. So it is a really a cycle that is leading studies to fail.

Q Do you have any suggestions as to how this can be addressed?

We need to think of solutions, otherwise we are in real trouble. In fact, we are already in trouble! Solutions could work in two directions. First of all, we need to improve the quality of centers taking part in studies, which can be done at two levels, selection (of centers) of course, and secondly, though this is more difficult, better training of investigators and patients before the study is done. There should definitely be more efforts in ensuring that the centers taking part in these studies are performing at top level. The second point, which goes along with the first, is that if we improve diagnostic and assessment procedures, we may not need so many sites. By doing a study at well-trained and experienced centers, we may remove a lot of confounders and achieve success with a sample size that is just one half of those enrolled in some recent trials.

Q Do you think this strategy will be cost effective?

Yes, it is probably worth it to pay specialized centers twice as much for example, rather than going for a large number of low-cost sites not adequately trained in this kind of research. To some extent, this could be facilitated by changing the rules of the game – in other words, changing existing trial designs. In fact, many experienced centers are in parts of the world where, for the ethical and practical reasons discussed before, it is increasingly difficult to randomize patients to placebo (or to an investigational, potentially ineffective treatment) in studies using the classical adjunctive-therapy design.

Q Do you think this is where novel trial designs can come into play to circumvent these ethical issues?

Potentially. What we are discussing now with regulators on both sides of the Atlantic, is whether we could change the paradigm. At present, we are being asked to randomize patients to placebo, often for up to 16 weeks or even longer, and often after an 8-week baseline, meaning that for 6 months people who could be benefiting from existing treatments that they have not yet tried could be trapped in a placebo arm and continue to have seizures, which is really unacceptable. Why don't we change the rules and switch to a novel design like time to nth seizure? Putting as an end point time to nth seizure means that patients who do not improve exit the study and patients who do well remain in the study. Patients will be more motivated to participate in studies if they know that if there is no improvement they will be taken out of the study. Conversely, if the investigational treatment does work well, they will be happy to stay on

long-term treatment and, therefore, long-term efficacy and safety data could be easily obtained. There are some drawbacks that need to be sorted out in this approach, but this design is very similar to what is being used now in the USA to assess efficacy of drugs as monotherapy.

Q Except that the design that you describe won't involve a historical aspect?

Absolutely, this is correct. In this instance there will be no historical controls.

Q That would mean such design would be statistically more meaningful?

For statistical demonstration of efficacy, I do not see any problem. One concern is that patients will need to be followed up for a sufficient period to obtain a comparative assessment of tolerability versus placebo. If all your patients on placebo come off very quickly, there is no control arm left in the double-blind period to compare the tolerability of the active treatment. This is one of the problems we need to address with this design, and we might have to settle for a compromise. For example, we may have to keep all patients in the study for 4 weeks, and then start implementing the exit criteria after that. This could ensure a minimum duration of follow-up to assess safety. Another option would be to add a third arm that will be randomized to receive an established active comparator. The third arm will be mainly used to assess comparative safety, where assessment of efficacy is done by comparison with the placebo arm, which drops off quickly if there is no response. So there are a variety of solutions, this is basically what is being discussed now.

Q How do you see the epilepsy trial landscape moving on from here in terms of next steps in trial design and increasing communication between academics, industry and regulatory bodies?

The epilepsy academics need to engage even more in discussion with regulators, because at the end of the day we all want efficacious drugs to be approved. We are on a common ground when we want to improve trial designs.

Q How would you suggest improved discussion between academics and regulatory bodies?

Well, the International League against Epilepsy, through one of its Task Forces has engaged with the FDA and with the European Medicines Agency and there are plans to organize a meeting with the two agencies to discuss best practice on study designs and put on the table some of the issues discussed above. We need to be aware of the drawbacks of the current designs and of the obstacles that the pharmaceutical industry faces in licensing drugs for epilepsy. This may result in no new drugs being developed, which would be a tragedy for people with epilepsy because the plague of pharmacoresistance today is almost as bad as it was 30 years ago. In fact, the AEDs licensed in the last 30 years have not substantially changed outcome in terms of seizure freedom, which is the ultimate goal. In a typical population refractory to older agents, the new drugs manage to control seizures in a maximum of 20–25% of patients, which means that 75% of refractory patients or more are still there with needs not met. If we discourage investment from industry by having regulatory requirements that are too difficult to meet, there is no hope for these people. We (the community) appreciate that we need to make sure that new drugs are tested properly and that all compounds that reach the market are efficacious and safe. Yet, we think there are improved ways by which we could safeguard those concerns as well as ethical principles and still get good drugs to the market in an efficient way. Outside the area of regulatory trials, I believe that in the future we will also be doing more 'effectiveness trials', that is trials that respond to the increasing demand by physicians to have sound comparative assessments of existing treatments under conditions resembling everyday use, using clinically meaningful end points. These studies would be complementary to regulatory trials, which only aim at demonstrating that a medicine is efficacious and safe, and usually do not measure comparative effectiveness.

Q Specifically from an academic perspective, do you think the academic community has potential to drive forwards the trial landscape?

Yes, absolutely. The community can work together in many ways in this regards. We can discuss with regulators and propose improved study designs. We can also put pressure on governments and funding agencies, including the European Commission and NIH, to alert them about the huge unmet needs in epilepsy. For example, the cost of epilepsy in Europe alone is 20 billion euros per year – governments need to be aware of this, and realize that leaving everything to the pharmaceutical industry is not the solution. Moreover, it is important to be aware that epilepsy is not a single disease. Many types of epilepsy are orphan disorders and although there may be some pharmaceutical companies willing to venture into developing orphan drugs, there is a clear need for academia to set up good multicenter studies to test treatments for the less-common epilepsy disorders, some of which are extremely devastating. If

such studies are done (by the academic community), this could eventually mean (regulatory) fast channels for such drugs, potentially translating into availability of more effective compounds in the market place. But for this we need to change the current situation and the way governments and multinational agencies support research for epilepsy and specifically the funding for clinical trials.

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