FLUOX-PMS editorial

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Fluoxetine (Prozac) is a familiar drug widely used in the management of anxiety and depression over the last 30 years. In 2016, 23 million prescriptions were issued in the US alone.[1] It also has a well understood safety profile. Could it be, and why should it be, postulated to have anti-progressive properties in multiple sclerosis (MS)? If true, it would be a victory for the repurposing movement, which takes a drug used for an original purpose, say aspirin as an analgesia, and applies it in another clinical setting, such as acute and preventative treatment for cardiovascular disease. There are obvious advantages: knowledge of the safety profile and avoidance of early-stage safety trials, all of which can lead to large savings, both financial and time.

Fluoxetine is classified as a selective serotonin-reuptake inhibitor (SSRI). In MS, previous work indicated that it can stimulate glycogenolysis, increase production of brain-derived neurotrophic factor and improve mitochondrial energetics. In an MRI spectroscopy study, fluoxetine increased white matter NAA/creatine ratio, which was postulated to indicate an improvement in axonal energy status.[2] Fluoxetine therefore ticked a number of the boxes to take it into a phase 2 trial, the results of which are reported in this issue of the *MSJ* as the FLUOX-PMS trial.[3]

The trial enrolled 137 subjects, with a 60:40 ratio of primary and secondary progressive MS, median EDSS 5.5/6.0 (active/placebo), and mean age 52 years. The study participants had to demonstrate clinical disability in the year prior to entry, and 25% were on first generation disease modifying therapies.

The primary outcome was 3-month sustained progression of disability defined as a ≥20% deterioration in either the timed 25-foot walk (T25FW) or 9-hole peg test (9HPT). Composite outcomes in MS have been embraced, because they increase the event rate, which increases trial power.[4] An observational PPMS study was used to derive the power calculations: 161 patients were followed for 2 years and the ≥20% unconfirmed deterioration rates were T25FW 46%; 9HPT 24%; either/or 56% (95%CI 48-64%).[5]

In the FLUOX-PMS trial the sample size was chosen to give 80% power to detect a reduction in disability progression of 25%, assuming a placebo progression event rate of 55%, with a projected 15% drop-out rate after 12 weeks, leading to an estimated sample size of 70/arm.

Ultimately, however: the trial entered 68 and 69 subjects in each arm, there was a drop-out rate of 20%, and the control arm progression rate was just under 40%, - all of which led to a substantial under-powering of the trial.

The primary outcome using the log-rank test (p=0.258) and Cox regression analysis (p=0.253) failed to show a difference between the two treatment arms. The Cox-regression analysis showed an unadjusted hazard ratio (increase in hazard for placebo over fluoxetine) of 1.253, accompanied by a wide 95%CI of 0.787 to 2.487. This means that the effect of placebo versus fluoxetine could be anything from a reduction of 21%, to an increase of 149%, in the hazard of progression. The authors rightly conclude that firm conclusions are impossible under this level of uncertainty.

This study therefore raises important issues regarding clinical trial design with implications for future trials. Why was the progression rate 40% and not the anticipated 55%? The original derivation sample was from a retrospective, observational cohort rather than a randomised prospective trial. That cohort also reported *unconfirmed* progression, while this trial utilized *confirmed* progression, the frequency of which is known to be lower. In addition it was collected 10 years ago, and on-trial progression event rates have declined over time.[6] For example, the placebo arm of a recent trial ASCEND (SPMS, n=887; treatment period 96 weeks), found a 35% progression rate in T25FW, 23% in 9HPT, and 48% in a multi-component composite which included EDSS.[7] Future trial planners using the T25FW and 9HPT might lean to 40% rather than 55% for a 2-year study, as well as study end-point completion rates of the order of 75%.[7] Indeed, contemporary progressive MS trials using a clinical primary outcome, have enrolled 3-12 times the number of subjects included in the FLUOX-PMS trial.[4]

There are other points that deserve attention. Firstly, only a subset of participants recorded MRI outcomes (n=74), more in the fluoxetine (55%) than the placebo group (45%). The possibility of selection effects somewhat down-weights the importance of this analysis. Furthermore, many clinical and imaging outcomes were collected, all of which were under-powered to detect a therapeutic effect. Should trials generally look to collect such large volumes of data? The results may be useful for designing later trials, but the additional cost and participant burden should be carefully considered. The focus of any trial should be a robust *primary* outcome conclusion: positive or negative.

Is that the end of the road for fluoxetine in progressive MS? Despite this trial's equivocal conclusions it seems likely. As referenced in this paper, initial reports of the MS-SMART trial [NCT01910259] found no difference in atrophy progression with fluoxetine, as well as a lack of benefit on major secondary clinical outcomes. Whilst it might still be possible that fluoxetine is indeed effective and this under-powered, clinical outcome-driven study prevented the

investigators from realizing that, studies like this remind us that sadly, there is no easy way to do clinical trials: the sample sizes must be robust and the calculations behind them realistic.

The trial signals a disappointing end to what appeared as a promising mechanism from original work over a decade ago.[2] It highlights the challenges in finding effective therapies for progressive MS and also reminds us of the demands of conducting clinical outcome-driven studies in a disease with variable and unpredictable progression.

References

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