Psychotropic drug development has largely stalled in recent times. Many novel ideas have appeared, but practical choices available to psychiatrists remain mostly unchanged. Two new medications are building up momentum to enter regular clinical use (Articles 1 & 2). Many of us have wished for an effective depot antipsychotic injection that lasts for a few months, and new longer acting formulations are now entering the market (Article 3). Predicting non-responders earlier during the course of treatment is always a clinical priority, and there are two interesting new studies in this regard (Articles 6 & 9). Optimum dosing of antidepressants and antipsychotics is often controversial, but its importance cannot be overlooked (Article 4 & 5). Clozapine is once again drawing attention with its better comparative efficacy, this time demonstrating it in routine clinical practice (Article 7). We have a more reliable variable to look for while monitoring clinical improvement in patients on antidepressants (Article 8). New research raises questions about the efficacy of interventions for negative symptoms (Article 9) and that of anti-inflammatory therapies for psychiatric disorders (Article 10).

1. ANY NEW MEDICATIONS EMERGING FOR BIPOLAR DEPRESSION?

Depressive symptoms in bipolar disorder are enduring, disabling, and challenging to treat. Treating bipolar depression with antidepressants alone remains controversial. Only quetiapine and lurasidone have been approved by The US Food and Drug Administration (FDA) for bipolar depression. Neurochemical evidences support the idea that enhancing dopamine may improve bipolar depression, and hence partial dopamine agonism is an option. Cariprazine is an atypical antipsychotic with partial agonist activity at dopamine 2 and 3 receptors, similar to aripiprazole. FDA has recently approved it for both schizophrenia and bipolar disorder (manic and mixed episodes). A previous phase 2 study had failed to prove its efficacy in bipolar depression. However, the new study by Durgam et al. now gives us more hope.

This multicentre study was carried out in 88 locations, among 584 adult patients with bipolar 1 disorder, currently in depression, of at least four weeks but less than 12 months duration. After a washout period of one week, the patients were randomly allocated to eight-week double-blind treatment with placebo or cariprazine and a 1-week safety follow-up. Cariprazine was started at 0.5 mg and then increased to fixed doses of 0.75, 1.5, or 3.0 mg/day. 73% of the participants completed the study. Symptoms were statistically better against placebo in the 1.5 mg cariprazine group. The difference was identifiable from week 1 itself. At six weeks, half in the 1.5 mg cariprazine group responded, as opposed to one-third in the placebo group (OR=2.10,1.3-3.4). When only 20% of placebo group attained remission at week six, the corresponding figure for the 1.5 mg group was 37%
(OR=2.38, 1.38-4.09). The magnitude of the benefit seen is modest (NNT of 6), and similar to that observed in bipolar depression with quetiapine, lurasidone or olanzapine.

Serious adverse events were minimal in the active arm, and in fact, were more in the placebo group. Treatment emergent akathisia was seen in 15% of high dose (3 mg cariprazine) group. A dose related increase in akathisia was also observed.

This study suggests that cariprazine may be a short-term option in bipolar depression. Head-to-head study with an established agent would have given us more insights on cariprazine’s role in our current formulary. Some readers may wish to see further replication of the results, given that this is an industry study. Also, brief studies like this do not provide us any information on sustained benefit or long-term harms.

REFERENCES


2. NEW DOPAMINE PARTIAL AGONIST THAT IS EFFECTIVE IN PSYCHOSIS

Choosing an antipsychotic medication is an act of balancing side effects, cost, and efficacy. Dopamine (D2) partial agonism, as shown by aripiprazole, is one established mechanism to relieve psychosis. Problems can arise in the early stage of aripiprazole treatment due to side effects like akathisia, nausea, insomnia, or restlessness. Brexpiprazole, a new dopamine partial agonist with lower intrinsic activity at the D2 receptor, and stronger antagonism at the 5HT2A receptor, is expected to cause less of such problems.

In this industry-sponsored brief trial, Cornell et al.1 randomly allocated 636 adults in acute relapse or exacerbation of schizophrenia to receive placebo or 0.25 mg, 2 mg, or 4 mg of oral brexpiprazole. The primary efficacy measure was change in PANSS score from baseline to week 6. These patients were markedly ill at study entry, with an overall mean PANSS total score of 95. Patients in the 2 and 4 mg brexpiprazole groups had statistically significantly greater mean improvement in symptom score at week 6. This advantage reached statistical significance at week 1 in the 2 mg group and at week 2 in the 4 mg group. NNT for response (30% improvement in PANSS total score or improvement in CGI rating by 1 or 2) were 6 for 2 mg and 7 for 4 mg of brexpiprazole. However, its 0.25 mg dosage did not have any significant effects on any of the efficacy measures.

Akathisia was more frequently reported in the 2 mg and 4 mg brexpiprazole groups (4.4% and 7.2%, respectively) than in the placebo group (2.2%). Activating effects (restlessness, insomnia, anxiety) and sedating effects (somnolence, fatigue, sedation) were similar to or lower than the rates in placebo group. Brexpiprazole caused moderate increase in body weight — An increase in body weight of 7% from baseline at any visit was seen in 9% of the 2 mg and 4 mg brexpiprazole groups, in contrast to 4.4% of the placebo group. There was no evidence of significant adverse effects on metabolic measures.

It is assumed that the intrinsic D2 activity of brexpiprazole lies between that of aripiprazole and D2 antagonist antipsychotics. Its profile on 5HT also makes it closer to other SGAs than aripiprazole.

Absence of an active comparator makes it difficult to predict whether brexpiprazole has meaningful benefits compared to existing agents, especially aripiprazole. It is also worth remembering that an earlier trial showed only the 4 mg to be effective against placebo.2 Future of the claim that brexpiprazole will occupy the space between
Aripiprazole and SGAs (in relation to relative side effects) would depend on further head-to-head trials.

REFERENCES


3. How effective is three-monthly paliperidone depot injection?

Poor medication adherence is a common reason for relapse in psychiatric disorders. Even though RCT evidence does not consistently show that depotss are superior to oral medications in efficacy, they are immensely beneficial in situations where nonadherence is very likely. Selection bias, i.e. the phenomenon whereby individuals likely to be non-adherent with prescribed treatment are generally less likely to be recruited to RCTs, may be one explanation for this lack of difference.

Paliperidone, an atypical antipsychotic, is available in monthly injectable form. A new formulation of this medication is now tested for administration every three months. Adults with schizophrenia recruited to this international study initially completed a screening and an open label phase. Patients who tolerated and remained stable on monthly injection during the open label phase (17 weeks) entered the maintenance phase with the 3-month preparation. Patients who remained well on the 3-month injection (n= 305) were then randomized to placebo or the 3-month injection. Dose of injection was 3.5 times of the once monthly dose the patient was receiving. The study revealed a significant difference between the treatment groups for time to relapse of schizophrenia symptoms, in favor of 3-month paliperidone palmitate (hazard ratio = 3.45; 95% CI= 1.73-6.88). 23% patients in the placebo group and 7% in the 3-monthly paliperidone group relapsed during the double blind phase. The study was terminated early due to clear benefits shown at interim analysis. The median duration of receiving placebo in the double-blind phase was 146 days. Compared to the placebo, headache (9% vs. 4%), weight gain (9% vs. 3%), nasopharyngitis (6% vs. 1%), EPS (8% vs. 3%) and akathisia (4% vs. 1%) were more common in the 3-monthly injection group.

There is considerable dosing dilemma with depot antipsychotics. Carpenter et al. have previously shown that there was no difference in clinical outcome when fluphenazine was given 6-weekly or 2-weekly. Long-term studies alone can answer questions on optimum depot dosing strategies.

This study shows that patients who tolerated and remained stable, initially on monthly paliperidone depot and then on three monthly depot, would benefit from continuing with three monthly depot as opposed to stopping the depot. Patients receiving placebo were nearly four times more likely to relapse. This is unlikely to surprise clinicians. More important question in clinical practice is whether the 3-monthly injection is more efficacious than the monthly injection. Nevertheless, the progress in bringing formulations that can be given less frequently, without much additional side effects burden, is a welcome one.

REFERENCES


4. WHAT ARE THE DOSE EQUIVALENTS FOR SECOND GENERATION ANTIPSYCHOTICS?

In day-to-day clinical practice, one commonly decides to switch a patient from one antipsychotic to another. To do that effectively, one has to know the comparable doses of the different agents concerned. Such information is also important in head-to-head control studies where you want to see fair trial, with comparable doses being used. Many methods are there to compare doses of different medications within a class. This includes using minimum effective dose, ‘near to maximum’ dose, maximum licensed dose, or daily defined dose.\(^1\) The classical method, known as the Davis method, is to use the mean dose from flexible dose RCTs to calculate doses that were equivalent to chlorpromazine.\(^2\) So far, no one has done such an analysis on Second Generation Antipsychotics (SGAs).

Leucht et al.\(^3\) collected all double blind, flexible-dose studies on SGAs, chlorpromazine, and haloperidol in acutely ill patients with schizophrenia. In all these studies, the dosing was based on clinical response, without knowing which specific medication was being administered — hence the resulting average dose can be considered the optimum mean dose for that group of patients. The authors calculated the olanzapine equivalent dose by dividing the weighted mean dose of the drug by the weighted mean olanzapine dose.

The analysis found that 10 mg olanzapine is equivalent to 380 mg amisulpride, 14 mg aripipazole, 9 mg asenapine, 389 mg chlorpromazine, 306 clozapine, 7 mg haloperidol, 323 mg quetiapine, 4 mg risperidone, 132 mg zotepine and 8 mg ziprasidone.

One major limitation of the Davis method is that it depends on clinical trial dosing which is decided on predefined dose ranges. Some trials may have used higher or lower dosing — This may affect the calculation, and titration of all possible doses is never feasible in such RCTs. The authors tried to overcome this limitation by including only those RCTs that had included the target dose ranges suggested by an international expert consensus.

REFERENCES


5. HOW MUCH IS A “GOOD DOSE” OF AN SSRI?

What is the optimum dose of SSRIs to treat depression? When confronted with partial benefit, dose escalation within maximum possible dose is the suggested strategy, of course if tolerated. Is there good quality evidence to say that higher doses lead to better treatment response?\(^2\)

A meta-analysis of studies that compared SSRIs with placebo on short term treatment of unipolar depression was done to answer this question.\(^1\) Forty studies covering 10,039 adult patients with major depressive disorder were included in the analysis. For all included studies, depression ratings were available for at least three time points.

Six different SSRIs were studied in the included trials. Incremental SSRI benefit was greatest in the first week, and gradually declined in magnitude as time progressed. Meta-regression demonstrated a significant association between SSRI dose (in imipramine equivalents) and efficacy of SSRIs, measured as the odds ratio of treatment response. When the SSRI dose was examined in dosing categories rather than as a continuous variable, a significant effect of dose still remained.

A small, but significant positive association was seen between higher dose and efficacy. This significant association between SSRI dose and efficacy was demonstrated in multiple methods of analysis.
Higher dose was associated with both a lower likelihood of all cause dropouts and a higher likelihood of dropouts due to side effects. However, the benefits in efficacy flattened out beyond 250 mg imipramine equivalent dose (i.e., very high doses). The greatest efficacy of SSRIs was observed in the dosing range of 200–250 mg imipramine equivalents. (100 mg of imipramine is considered equivalent to 120 mg of sertraline, 100 mg of fluvoxamine, 20 mg of paroxetine, 20 mg of fluoxetine, 33.3 mg of citalopram, or 16.7 mg of escitalopram.) One could argue that 200–250 mg imipramine equivalent doses — more than 250 mg sertraline, 60 mg citalopram, or 30 mg escitalopram — are too high for some SSRIs. In clinical practice, it is important to make a judgment on partial response and see whether higher doses of the same antidepressant can be tried before switching to another one. This metaanalysis supports the idea of trying higher ends of recommended doses in such cases.

The evidence produced here applies only to partial responders. Findings of this study would assure clinicians who face a partial response to use higher doses, with close monitoring of side effects, to extract maximum possible benefits from each antidepressant.

REFERENCES


6. IS EARLY IMPROVEMENT A PREDICTOR OF LATER RESPONSE TO ANTIPSYCHOTICS IN SCHIZOPHRENIA?

After initiating an antipsychotic, how long do you wait to see whether it is working? In the past we were more likely to wait for many weeks to allow time for the medication to ‘kick in’ and produce the benefits. A metaanalysis1 questioned this practice by showing that most symptom reductions occur in the first week. Leucht et al.2 later concurred with this finding with support from longer-term data. Since then, most studies have suggested that early improvement may predict later response. However, sufficient clarity is not there regarding the time frames of this initial response. The American Psychiatric Association (APA) suggests 2-4 weeks to get an initial response; The Patient Outcome Research Team (PORT) and the World Federation of Societies of Biological Psychiatry (WFBP) recommend waiting at least two weeks; and The National Institute of Clinical Excellence (NICE) and the British Association of Psychopharmacology (BAP) suggest 4-6 weeks of an adequate dose before switching.

Samara et al.3 used a novel metaanalytic technique - diagnostic test review - to see whether nonresponse by week 2 is predictive of treatment failure. The index test is a predefined degree of non-improvement at week 2 and the reference standard is nonresponse at a later stage. The authors included all studies that identified the responders to an antipsychotic, using the degree of improvement in overall symptoms (PANSS or BPRS) of schizophrenia at two weeks. Non-improvement was defined as less than 20% reduction in the total scale score from baseline to two weeks, while non-response was defined as less than 50% reduction of the total scale score from baseline to endpoint. 59 articles, corresponding to 34 studies with 9,460 participants, were included in the analysis. Results showed that, at endpoint, 86% of all responders could be identified as such at two weeks and the reference standard is nonresponse at a later stage. The authors included all studies that identified the responders to an antipsychotic, using the degree of improvement in overall symptoms (PANSS or BPRS) of schizophrenia at two weeks. Non-improvement was defined as less than 20% reduction in the total scale score from baseline to two weeks, while non-response was defined as less than 50% reduction of the total scale score from baseline to endpoint.
The findings of this analysis should be applied only to patients who have received target doses for at least two weeks. This analysis reminds us of the importance of close monitoring in early stages of the treatment to make the best decisions early on.

REFERENCES


7. ARE PATIENTS STARTED ON CLOZAPINE MORE LIKELY TO REMAIN WELL IN ROUTINE CLINICAL PRACTICE?

Standard antipsychotics fail in 30% of schizophrenia patients. The only medication effective in treatment-resistant schizophrenia is clozapine. Clozapine-monitoring systems have been highly effective in virtually eliminating deaths due to agranulocytosis. Though this should reassure prescribers, clozapine still remains underused.

Stroup et al. adds to the evidence base for clozapine’s well-established advantage by proving its usefulness for a routine clinical practice cohort. They studied the effectiveness and safety of starting clozapine against initiating standard antipsychotics, using a retrospective cohort analysis of schizophrenia patients in routine practice. The US National Medic Aid data (insurance scheme) from 2001-2009 were used. The cohort comprised of patients who have received treatment for schizophrenia in the past, and are currently in active treatment with medications, and have been recently started on an antipsychotic they haven’t received in the past one year. All the patients have had at least one admission, and had been prescribed at least two antipsychotics in the past. Psychiatric hospitalization was the primary outcome measure.

Patients started on clozapine were not different from those prescribed standard antipsychotics. During the one year after the initiation of treatment, those on clozapine had significantly more OP visits, more psychotherapy visits, and a similar number of psychosocial service contacts compared to those on standard antipsychotics. The clozapine group had lower rates of hospital admission for mental disorder (hazard ratio=0.78, 95% CI=0.69–0.88), and were less likely to discontinue the medication (hazard ratio=0.60, 95% CI=0.55–0.65). They were also less likely to need an additional antipsychotic (hazard ratio=0.76, 95% CI=0.70–0.82). As expected, clozapine-treated patients were more likely to develop diabetes (hazard ratio=1.63, 95% CI=0.98–2.70), hyperlipidemia (hazard ratio=1.40, 95% CI=1.09–1.78) or intestinal obstruction (hazard ratio=2.50, 95% CI=0.97–6.44). There was no difference in myocarditis, IHD, agranulocytosis, or mortality rates between the two groups.

This analysis shows that, in individuals with resistant psychosis, clozapine is more effective than a standard antipsychotic in reducing the risk of hospital admission and antipsychotic discontinuation. The resistance criteria included hospitalization to initiate new medications. It is unclear how the cohort is different from resistant patients who are treated without hospitalizations. We also do not know how severe the symptoms were, as clozapine may have been started only for those with severe degree of illness. Also, patients on clozapine are more likely to be assessed for certain side effects (surveillance bias) and thus over-reporting is likely in this group. The US Medic Aid database used is perhaps not sensitive enough to detect such effects.

Underutilization of clozapine is a problem in many countries. Regular prescription audits and intense educational efforts are likely to improve this situation. Not considering clozapine in resistant
schizophrenia is a ‘clinical crime’ against individuals who live in perpetual misery due to disabling symptoms.

REFERENCES


8. ARE ANTI-INFLAMMATORY THERAPIES VIABLE TREATMENTS FOR PSYCHIATRIC DISORDERS?

The idea that inflammation may play a role in psychiatric disorders is increasingly supported by evidence. Miller and Raison1 examine the future of anti-inflammatory strategies in psychiatric disorders.

It is still unclear whether anti-inflammatory strategies are clinically beneficial or not. A recent review highlighted the lack of clear benefits with anti-inflammatory drugs like aspirin and celecoxib in schizophrenia.2 The largest and most recent metaanalysis assessing the efficacy of anti-inflammatory agents in depression found that these medications reduced depressive symptoms significantly (standard mean difference: −0.34; 95% CI −0.57 to 0.11), without causing more gastrointestinal or cardiac side effects.3

We know that inflammation is shown by only certain subgroups of patients within specific psychiatric disorders. There are not many trials that have examined the role of anti-inflammatory agents in such selected subgroups. One study showed that baseline inflammatory markers can predict response to treatment in resistant depression.4 Another recent study found that CRP is predictive of differential antidepressant response to SSRIs or TCAs.5 It is also possible that using anti-inflammatory agents in those without inflammatory activity may do more harm than good.

In psychiatric disorders, inflammation targets specific subcortical and cortical circuits known to mediate anxiety, alarm and arousal. This might have some evolutionary significance — i.e., shutting of energy expenditure to fight infection while being vigilant against attack. However, it is also important to acknowledge other possibilities. For example, the psychiatric disorder itself may cause the inflammation, and successful treatment of the disorder may explain the observed reduction in inflammatory markers. Similarly, non-inflammatory actions of anti-inflammatory medications might be the actual reason behind reduction in psychiatric symptoms. New clinical trials, carefully designed to address the pitfalls of previous studies, are needed to test such possibilities.

This field is still in its infancy and hopefully would offer clinicians more options in due course. Given the limited treatment options we have for various psychiatric conditions, there is no doubt that this particular strategy has to be pursued with vigor.

REFERENCES


9. DOES ANYTHING WORK IN NEGATIVE SYMPTOMS OF SCHIZOPHRENIA?

Negative symptoms account for much of the functional disability associated with schizophrenia. Primary negative symptoms remain very difficult to treat. The benefits of SGAs, though claimed, have not been consistent. There are around 40 different antipsychotics in the market, and it is important to assess whether any of these are effective for negative symptoms.

All placebo-controlled randomized trials conducted among adults with schizophrenia or schizoaffective disorder were analyzed by Fusar-Poli et al. Data from 146 published articles, with a total population of 6503 patients in the treatment arm and 5815 patients in the placebo arm, were analyzed. Mean duration of intervention was 12 weeks. The mean % change in treatment group was 16%, while the control group changed on average by 8%. Most interventions assessed - SGA, antidepressants, glutamatergic medications and psychological treatments - produced statistically significant symptom reduction. First generation antipsychotics (FGA) and brain stimulation therapies did not have any such effect.

Is this a meaningful benefit? In terms of CGI-S (Clinical Global Impression Scale) scores, an improvement by one “severity step” corresponds to approximately 30%–40% improvement of BPRS score and approximately 30% improvement in PANSS score. When this criterion was used to see whether the medication groups really benefitted, none of the above groups showed any statistically significant benefit.

It looks like none of our present treatments reduce negative symptoms to a meaningful degree. Management of negative symptoms remains a major challenge for clinicians.

REFERENCES


10. EARLY DECREASE IN SADNESS OR INCREASE IN JOY: WHICH BETTER PREDICTS ANTIDEPRESSANT RESPONSE?

Lack of early improvement with an antidepressant is often predictive of later non-response. Up to 60% of the improvement that occurs during antidepressant treatment happens during the first two weeks. Usually, we use the total score on a rating scale or general clinical impression of how less the individual experiences the core symptoms to know whether early improvement is occurring. It is also possible that we could look at positive emotional experiences rather than decrease in negative states. Is it possible that changes in positive emotions could be more predictive of later response or remission?

Authors of this study assessed a large sample of moderate to severely depressed outpatients (N=2351) treated with agomelatine (25-50mg), and rated changes in frequency of their emotions (sadness and joy) at baseline and at week 2, to compare the ability of the changes in those emotions in that period to predict treatment response at week 6.

At baseline, 23% of patients never experienced joy during previous week, and 71% reported experiencing joy ‘sometimes’. After six weeks, 56% met the response criteria and 25% achieved remission. Increase in joy in the first two weeks was more associated with treatment response than decrease in sadness (85% Vs. 58%). Joy had a higher positive predictive value (71% Vs. 66%). Among
non-responders, 4/10 had decreased sadness at week 2, but only 1/7 rated increased joy.

The study shows that joy and sadness are not necessarily correlated—i.e., patients are not feeling joy because they are becoming less sad. Experiencing joy early on is more predictive of treatment response than a decrease in sadness. Geshwind et al.² too had reported similar findings. This idea that joy and sadness are independent is interesting. The data also suggest that these perhaps reflect two different factors.

Most clinicians would argue that, in day-to-day clinical practice, they focus on the emergence of the ability to enjoy or experience pleasure as much as they do on decrease in sadness. On the other hand, the commonly used rating scales do not have questions on positive emotions. From a therapy perspective, identifying, reflecting and broadening positive emotional experiences among depressed individuals are important. This study reminds us about the need to focus on positive emotional states while assessing progress with antidepressants.

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