

Happy birthday neuroleptics! 50 years later: *la folie du doute*

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Summary – Given that we are celebrating the 50th birthday of neuroleptics introduction in psychiatry, the author proposes to take a look at certain results related to therapeutic practice. After a brief chronological literature review of the clinical practices and theoretical models that have controlled drug treatment of schizophrenia, the author presents a critical review of four meta-analyses. Since Delay, Deniker and Harl's initial report, the story of neuroleptics comprises several periods. In 1963, the hyper-dopaminergic theory of psychoses was proposed. Another period began with models mainly based on the serotonin/dopamine relative blockade receptor hypothesis. More recently, a new framework to understand the differential effect of antipsychotics is related to the appropriate modulation (e.g., fast dissociation) of the D2 receptor alone. The concept of atypicality has become a new vista for research and to market new compounds. However, after 50 years of neuroleptic drugs, are we able to answer the following simple questions: Are neuroleptics effective in treating schizophrenia? Is there a difference between atypical and conventional neuroleptics? How do the efficacy and safety of newer antipsychotic drugs compare with those of clozapine? Actually, the answers yielded by these simple questions by meta-analysis should elicit in us a good deal of humility. If we wish to base psychiatry on evidence-based medicine, we run a genuine risk in taking a closer look at what has long been considered fact. Each psychiatrist must continue to be critical, sceptical, optimistic (not overoptimistic) and to learn in order to integrate the positive aspects of our growing knowledge base. © 2002 Éditions scientifiques et médicales Elsevier SAS

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The first trial using neuroleptics for psychiatric purposes was supposed to have taken place on 9 November 1951 at Villejuif psychiatric hospital in Paris [6]. It consisted of the intake of chlorpromazine by a staff psychiatrist of the hospital in order to test its potential emotional effect. Actually, antipsychotic drugs were used for the first time in France in 1952 by the Val-de-Grace hospital team (a military hospital where famous politicians of the Republic are treated) [22], then by the

team of Sainte Anne hospital in Paris [2-3,7-19,21]. Synthesised and tested by Charpentier and Courvoisier in 1950, chlorpromazine (Rhone Poulenc) was used for the so-called *hibernation artificielle* in anaesthesia and surgery by Henri Laborit [1,26,32]. This marine surgeon noticed the tranquillising effect without sedation induced by this drug and predicted an interest for psychiatric diseases. At the time of neuroleptics' discovery, their mechanism of action was totally unknown. In

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1957, dopamine was identified as a central neurotransmitter. It was only in 1963 that the dopamine receptor blockade was recognised as the main effect of neuroleptics [4]. Even as the debate around the 5HT2/D2-ratio hypothesis is still ongoing [30,31,34], we have all noticed the rebirth of the dopamine hypothesis [24]. A hypothesis based on the interesting *k*-off differential component of binding, which postulates that the effect of a drug is proportionate to the kinetic rate of onset (*k*-on) and offset (*k*-off) of the drug binding to the receptor. Contrary to the multireceptor hypotheses, the predominant predictor of atypicality of antipsychotics is fast dissociation from the D2 receptor which is clearly present with clozapine and quetiapine. Given that all the antipsychotics have a quite similar *k*-on, only a difference at a rapid dissociation from the D2 receptor leads to the atypical antipsychotic effect [25]. However, at the beginning, Delay and Deniker progressively developed the notion of neuroleptics, giving a definition with five points: *état d'indifférence*, antipsychotic action, induced parkinsonism, a main sub-cortical effect. Originally, typical meant inducing extrapyramidal symptoms. Afterward the chemical family of phenothiazines succeeded butyrophenones and others such as dibenzodiazepines “where clozapine is the head.” The term typical varies according to authors, dosage and marketing [29,33].

Given that we are celebrating the 50th birthday of neuroleptics' introduction in psychiatry, could we take a look at certain results related to therapeutic practice? Evidence-based medicine (EBM), as the term itself suggests, is medicine resting on strong scientific proof. For some time now, EBM has been growing in importance in a number of areas, including pedagogy, where it is changing how medicine is taught and bringing about a rationalisation of good clinical practice. Psychiatry has embraced this trend and, for the purpose of self-examination, resorts to meta-analysis, that is, a procedure for statistically processing studies as data. In other words, it is a method for reviewing and assessing research literature. In a sense, meta-analysis is analogous to experimental research in its aim to statistically integrate and analyse results. Its study population consists of all published studies on a given topic. Statistical analyses are carried out on this population in order to verify various assumptions, which most often have to do with treatment evaluation concerns. Meta-analysis can be broken down into six steps. First, a research question must be formulated, for example: Are atypical antipsychotics safer and more effective than conven-

tional neuroleptics? Second, a complete review of the relevant literature must be undertaken. Third, all data entries and variables must be coded (e.g., number of participants, duration of double-blind period, dosage of haloperidol). Fourth, an effect size index must be established. Fifth, a statistical analysis of the effect size distribution must be carried out. Finally, results must be interpreted. After 50 year of neuroleptic drugs, are we able to answer the following simple questions: Are neuroleptics effective in treating schizophrenia? Is there a difference between atypical and conventional neuroleptics? How do the efficacy and safety of newer antipsychotic drugs compare with that of clozapine?

Are neuroleptics effective in treating schizophrenia? A recent meta-analysis conducted by Thornley and Adams [35] examined the content and quality of 2000 controlled trials completed from 1948 to 1997. They sought as much data as possible by searching Biological Abstracts, CINAHL, the Cochrane Library, Embase, LILACS, Psychlit, PSYINDEX, Medline and Sociofile. In all, this represented 30,000 electronic reports and 6000 articles. They then coded the quality of the studies according to various criteria, including double-blindness, randomisation and duration. On this basis, only 1% of the studies was deemed to be of good quality on a scale of 1 to 5. On-third received a rating of 2, which indicated qualitative deficiencies. The poorest studies had been conducted in the United States, but the authors noted an improvement in quality over time. The average quality rating was a mediocre 2.5. The average number of participants in the trials was 65, and only 1% of the studies had sufficient statistical power. Only 3% of the trials had a sample size of 150 or more, which is necessary to demonstrate an inter-group difference of 20%, and 50% had fewer than 50 participants. The duration of 54% of the trials was less than 6 weeks; only one-fifth lasted 6 months. Also, 25% of the studies did not utilise an instrument of measure to assess changes. In the remaining sample of studies, 640 different instruments of measure were identified. Thornley and Adams concluded: “The consistently poor quality of reporting is likely to have resulted in an overoptimistic estimation of the effects of treatment”. The authors also stressed that the unusually large number of rating scales used and the limited time of studies may result in misleading, significant findings. For 50 years, chlorpromazine has been known by its French trade name Largactil®, which means in French large action. Perhaps we should change it to ‘Petitactil’ or ‘Smallactil’?

Are atypical neuroleptics more effective than conventional ones? In 1999, Leucht et al. [27] published a meta-analysis on efficacy and extrapyramidal side effects of the new antipsychotics. Their findings showed that the new drugs are more effective than placebo but the magnitude of the effect is moderate. When negative symptoms were studied, new antipsychotics were more effective than placebo; however, so was the conventional neuroleptic haloperidol. In addition, although in direct comparisons some atypical drugs showed slight superiorities in terms of negative symptoms, it is unclear whether their better performances relate to primary or only secondary negative symptoms. The authors further noted that the clearest superiority was for atypical drugs with fewer EPS, a result biased by mostly comparing it to haloperidol, which in many cases was given in high doses (20 mg/day).

A more recent meta-analysis completed by Geddes et al. [20] looked at 52 controlled trials involving 12,649 patients overall. The authors examined trials comparing amisulpride, clozapine, quetiapine, risperidone and sertindole against conventional drugs (haloperidol or chlorpromazine). They searched for data from no later than 1 December 1998, on Medline, Embase, Psyclit and the Cochrane Library. With the help of a panel of experts, they also tracked down unpublished studies and asked pharmaceutical companies for access to their unpublished data (companies were solicited twice at a 1 month interval). In particular, the authors examined efficacy variables such as BPRS and PANSS scores, as well as dropout rates and side effects. They also performed regression analysis using haloperidol equivalent dosage as the predictive value. The results showed that the average duration of the studies was 6.5 weeks and only five exceeded 1 year. They observed that many of the perceived benefits of atypical antipsychotics are really due to excessive doses of the haloperidol or chlorpromazine used in the trials, concluding that "atypical antipsychotics have a similar effect on symptoms to conventional antipsychotics at an average dosage of < 12 mg/day of haloperidol." The authors then described the results for each medication and found that patients receiving atypical antipsychotics did not have lower dropout rates or better responses than patients receiving the optimal dose of conventional antipsychotics and reached the following general conclusion: "Conventional drugs should remain the first treatment." This meta-analysis is a supplementary argu-

ment to continue the effort in order to demonstrate that psychopharmacological trials have to be clinically meaningful.

The degree to which a new compound is clinically superior to a conventional antipsychotic will require further a priori hypotheses based on conceptual frameworks that are clinically meaningful [33]. It is interesting to note that, despite the long-term course of schizophrenia, the duration of treatment evaluation in the above meta-analysis was very short. It cannot be denied that there is currently no compelling evidence on the matter, where 'long-term' is concerned. Kapur and Remington commented recently that most of their patients, who do not pay for medications, prefer atypical antipsychotics because of the lower incidence of side effects [23]. They reported that the combination of the findings by Geddes plus their own clinical experience "leave the clinician on a tightrope act between the persuasiveness of the marketing claims, the precise but somewhat myopic results of idealised clinical trials and the complex realities of clinical practice."

How do the efficacy and safety of newer antipsychotic drugs compare with that of clozapine? The Cochrane Schizophrenia Group has performed several meta-analyses addressing the efficacy of typical and atypical antipsychotics. In an attempt to compare newer antipsychotic drugs to clozapine, the authors [36] identified eight blinded randomised controlled trials that compared newer antipsychotic drugs with clozapine (795 patients) after searching in publications in all languages from Biological Abstracts/BIOSIS (1980–1999), the Cochrane Schizophrenia Group's Register of Trials (1998), the Cochrane Library CENTRAL Register (Issue 4, 1999), EMBASE (1980–1998), MEDLINE (1966–1999), LILACS/CD-ROM (1998), and PsycLIT/PsycINFO (1974–1999). In addition trials were sought from recent conference proceedings and reference lists of included papers. Authors of recent trials and the manufacturers of clozapine, iloperidone, olanzapine, quetiapine, remoxipride, risperidone, sertindole, ziprasidone and zotepine were contacted. Duration of trials was from 4 to 18 weeks. Sample sizes ranged from 20 to 273. The study concluded that newer antipsychotics and clozapine did not differ when using a clinical global index, including positive and negative symptom improvement. But this result was due to the small number of studies conducted, and therefore has to be interpreted with caution. On the other hand, they found that the adverse effects differed, clozapine produced more fatigue, hyper

salivation, nausea and orthostatic dizziness, while new atypical antipsychotics with the exception of olanzapine produced more extrapyramidal symptoms. The reviewers finally concluded that: “The equal effectiveness and tolerability of new atypical drugs in comparison with clozapine is not yet demonstrated.” The review emphasised that trials of sufficient power, with longer duration, measuring clinically important outcomes, are needed to assess the true comparative clinical effectiveness, tolerability and cost-effectiveness of newer drugs in relation to clozapine. A more recent meta-analysis [5] based on seven studies comparing clozapine to a typical antipsychotic revealed that treatment-resistant schizophrenic patients have more favourable outcomes on clozapine. However, the effect size on overall psychopathology were highly variable, ranging from 0.14 to 0.81. In addition, there were no significant treatment effects for clozapine over conventional antipsychotics on scores for the BPRS positive symptom subscale.

The answers yielded to these simple questions by meta-analysis should elicit in us a good deal of humility. One thing is certain: if we wish to base psychiatry on EBM, we run the genuine risk of taking a closer look at what has long been considered fact.

This anniversary gives us the right to ask if antipsychotics work, but am I celebrating this in a naive manner? First of all, what is efficacy? Should we not mention that this means in clinical trials a 20–40% reduction of positive symptoms on a standardised scale at a minimum? One point implicit in our critical review of meta-analysis is whether significant reduction of positive symptoms really means that neuroleptics work that well. This is certainly worth debating. We now know, for example, as we did not 50 years ago, that positive symptoms do not correlate with outcome, but negative and cognitive symptoms do. Furthermore, the new antipsychotics are supposed to target these symptoms and improve them better than neuroleptics. One could usefully point out that none of these agents causes schizophrenia to go into remission, so there is still a long way to go on efficacy. We must mention these important deficiencies in the neuroleptics’ and atypicals’ efficacy profile.

At this point in time, responsibility and honesty suggest we accept that a large number of our therapeutic tools have yet to be proven effective in treating patients with schizophrenia. Psychiatrists must above all continue to doubt and remain critical. We must also militate in favour of the publication of negative results,

because their inaccessibility modifies our body of knowledge as a whole, typically introducing a bias in favour of the new drugs. When faced with a patient with schizophrenia, who has come expecting to receive a service, the clinician must implicitly and explicitly process a host of information, weigh it critically and then propose the result of a compromise. After all, one of the clinician’s functions is to reassure and inform the patient. If he bases himself on meta-analysis, he will certainly be honest, but the chances are good that he will not be reassuring. Hans Lehman, who was the first psychiatrist to introduce neuroleptics in North America, in Montreal, Canada, wrote in an article titled “The history of the psychopharmacology of schizophrenia,” that effective treatment of schizophrenia was achieved only after the introduction of antipsychotic drugs in the 1950s and is still progressing [28]. Celebrating the 50th anniversary of neuroleptics and thinking about their efficiency, one cannot resist quoting Umberto Eco (apparently quoting Boscoe Pertwee, an 18th-century author) in *Kant and the Platypus*: “I used to be indecisive, but now I am not so sure.”

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