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Editorial

The New Atypical Antipsychotics

A lack of extrapyramidal side-effects and new routes in schizophrenia research

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The recent introduction of remoxipride, clozapine, and now risperidone has awakened interest in the clinical psychopharmacology of atypical antipsychotics. This editorial concerns pharmacological mechanisms of these drugs and their relative clinical efficacy.

The clinical efficacy of chlorpromazine was first discovered in the early 1950s (see Reynolds, 1992, for review); subsequent therapeutic research has had two main goals: to define the mechanism of efficacy; and to increase the therapeutic ratio of the drugs with respect to their extrapyramidal side-effects (which is why they are termed 'atypical').

The first aim has been largely achieved, and it is now clear that antipsychotic drugs exert their effects by blockade of dopamine D_2 receptors (e.g. Creese *et al*, 1976). However, blockade of D_2 receptors also predicts extrapyramidal side-effects. Moreover, negative symptoms generally do not respond to treatment with atypical antipsychotics. Therefore, efforts to produce atypical drugs have focused on either searching for an alternative site of action of a drug, or seeking more subtle ways of differentially blocking D_2 receptors.

Defining the term 'atypical'

Antipsychotics are screened for efficacy against a number of animal paradigms, including amorphine-induced stereotypy, amphetamine-induced hyperactivity, inhibition of intracranial self-stimulation, and conditioned operant behaviour (Janssen & Van Bever, 1978; Fielding & Lal, 1978). These effects are mediated by mesolimbic dopamine (DA) receptors (Kelly *et al*, 1975). But such drugs also block DA receptors in the striatum (Sanberg, 1980), causing immobility-reduced exploratory behaviour, and catalepsy (the animal equivalent of Parkinsonism).

Typically, classic neuroleptics have a low ratio between these effects, and animals become cataleptic at the same doses that also block mesolimbic systems. Thus most butyrophenones, phenothiazines, and butylphenpiperidines provoke catalepsy at doses close to their presumed therapeutic dose. The challenge is therefore to widen the ratio between these effects, to allow antipsychotic action without extrapyramidal side-effects (i.e. be atypical).

The simplest definition, then, is that an *atypical* antipsychotic is an effective neuroleptic that does not provoke catalepsy in rats or, in other words, has a wide therapeutic ratio for its antipsychotic effects and extrapyramidal side-effects, such that these are not seen at clinically effective doses. Early examples include clozapine, thioridazine and loxapine (Gerlach *et al*, 1975; Kramer *et al*, 1978). More recent introductions include the substituted benzamides, such as sulpiride and remoxipride (Hogberg *et al*, 1987) and most recently risperidone (Mertens, 1992).

The catalepsy test is an important paradigm non-presumptive of a relevant mechanism, and thus has been very useful in delineating a range of pharmacological mechanisms by which a drug can be atypical. Thus, clozapine is atypical because of its low propensity to block D_2 receptors (Pilowsky *et al*, 1992), and thioridazine is atypical because of its high intrinsic antimuscarinic activity (Miller & Hiley, 1974). The substituted benzamides are atypical because of low D_2 affinity but effective because of high *selectivity* to the D_2 family of receptors (Kohler *et al*, 1992), and risperidone may be atypical because of a protective effect of high 5-HT_2 blockade (Janssen *et al*, 1988).

Despite this, recently there have been attempts to redefine the term 'atypical' according to a putative mechanism. This is confusing, and Nutt (1990) has observed that the term is variably being used to describe drugs that do not sedate or cause extrapyramidal side-effects, drugs that do not cause depolarisation blockade, drugs that block D_1 rather than D_2 receptors, or drugs that block serotonin receptors. In order for empirical drug tests to open up hitherto unconsidered avenues of research and drug development, it is important to adhere to the original, non-specific definition. Such screening without presupposition of a pharmacological substrate is a useful dragnet to finding novel mechanisms. From a clinical standpoint, clinical atypicality would be defined by the low propensity to produce extrapyramidal side-effects and tardive dyskinesia relative to typical drugs like haloperidol and chlorpromazine,

as well as the low propensity to induce akinesia and hyperprolactinaemic effects.

Pharmacology of individual atypicals

Clozapine

Clozapine is the archetypal antipsychotic developed and known to be non-cataleptogenic since the early 1960s (Coward *et al*, 1989), and this is reflected in its clinical profile as a highly effective antipsychotic (Kane *et al*, 1988) with a low propensity to produce extrapyramidal side-effects (Claghorn *et al*, 1987). Clozapine is a relatively non-selective drug and it has proved difficult to pin down the reason for its atypicality.

Effect on dopamine systems

It was originally thought that clozapine, like other atypicals, has a preferential effect on mesolimbic rather than striatal dopamine systems (White & Wang, 1983). However, electrophysiological studies show that firing rates in both mesolimbic and striatal dopamine neurons are equally affected by clozapine and in a similar manner to haloperidol (Rebec *et al*, 1980). Its non-cataleptogenic and low profile of extrapyramidal side-effects are probably a result of its low affinity for D_2 receptors. Thus clozapine only weakly displaces ^{3}H-spiperone from D_2 sites (Kohler *et al*, 1981).

This has been confirmed *in vivo* in patients. Farde *et al* (1992), using positron emission tomography, have determined a threshold for D_2 occupancy by neuroleptic which predicts extrapyramidal side-effects at about 80% occupancy. Occupancies for clozapine patients were only in the range 30–60%. This then is sufficient to account for its lack of extrapyramidal side-effects – but how does it work?

Our group (Pilowsky *et al*, 1992) demonstrated that this low occupancy is not sufficient to account for its clinical effect. In this study, it was shown that a group of non-responders on classic antipsychotics had high D_2 occupancy and that a group of clozapine responders had low D_2 occupancy (two of the patients being scanned serially). Other candidates for clozapine's site of action then include not only D_1, D_4 5-HT_2, but also muscarinic and α receptors.

Farde *et al* (1992) have shown clozapine to have a higher occupancy at D_1 receptors than classic antipsychotics, although *in vitro* studies show it to be a modest inhibitor of D_1 binding. Moreover, other relatively ineffective compounds have higher affinity for D_1 sites (Andersen *et al*, 1986), and it has been suggested that there may be a D_1 bias *in vivo*.

Measures of dopamine metabolites in freely moving animals give some support to a D_1 preferential action of clozapine *in vivo* (Imperato & Angelucci, 1988). Studies with immediate early gene markers of synaptic activity do not support this (see later).

Recently, the D_2 receptor has been cloned and sequenced, which led to the revelation of further genetic subdivisions of the D_2 family, namely D_3 and D_4 (Sokoloff *et al*, 1992). Of these, the D_4 receptor has a uniquely high affinity for clozapine (Van Tol *et al*, 1991). In addition, these studies show that the D_4:D_2 affinity ratio for clozapine is higher than for any other antipsychotic. However, high affinity alone cannot indicate efficacy, and this is a difficult hypothesis to test because of the low abundance and limited distribution (frontal cortex hippocampus) of this receptor species.

Van Tol *et al* (1992) have found that there are polymorphic forms of the receptor, with a variant sequence (repeated severalfold) in an intracytoplasmic loop of the protein. The higher-fold repeats seem to have lower affinity for clozapine and low second-messenger coupling potential (Van Tol *et al*, 1992). We have tried to test the relevance of clozapine action at D_4 receptors by determining whether non-responsivity is associated with higher-fold repeats. In an initial study of 84 patients, we have found this not to be the case (Shaikh *et al*, 1993). It is also apparent that a relatively low-efficacy antipsychotic, loxapine, has even higher affinity for D_4 receptors than clozapine. Thus the relevance of D_4 receptors to clozapine's action remains unanswered.

Effect on 5-HT systems

Serotonin type-2 (5-HT_2) receptors are also a strong candidate for clozapine's antipsychotic action. 5-HT_2 receptors are highly enriched in medial prefrontal cortex (a candidate region for the site of the neurochemical abnormality; e.g. see Weinberger, 1987) and clozapine has very high affinity for these sites in radioligand studies (Altar *et al*, 1988). Clozapine also has potent effects on neuronal firing rates when applied iontophoretically to medial prefrontal cortex (Ashby & Wang, 1990). In addition, pure 5-HT_2 antagonists have been reported as antipsychotic in open studies (Reyntjens *et al*, 1986). Neuroendocrine studies and metabolite studies on 5-HT_2-dependent responses suggest that clozapine also has potent effects *in vitro* (Meltzer, 1989*a*). Studies in patients have shown that high ratios of 5-HIAA over homovanillic acid retrospectively predict good response to clozapine.

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Meltzer (1989*b*) has argued that the unique profile of clozapine relates to parallel effects of the drug on 5-HT_2 and DA_2 systems. Most recently, however, clozapine has also been recognised as having high affinity at 5-HT_{1C} (Canton *et al*, 1990) sites, which are also enriched in prefrontal cortex (Hoyer *et al*, 1986). So there are other potential routes to clozapine's 5-HT-dependent effect, and the effect of clozapine on this complex receptor system needs to be fully catalogued before any firm conclusions can be drawn.

Anatomical studies

There has been immense interest in the study of immediate early gene expression (c-fos and c-jun) as markers of synaptic activity, and gene expression has been useful as a sensitive indicator of the anatomical localisation of drug effects (e.g. Graybiel *et al*, 1990).

Studies with clozapine have been used to illuminate their site of action and possibly help to determine the receptor action relevant to its functional effects. Robertson & Fibiger (1992) have shown that, unlike haloperidol, clozapine fails to induce c-fos in the striatum, but, like haloperidol, induces activity in the nucleus accumbens. Clozapine, however, is unique in its ability to activate lateral septum and medial prefrontal cortex. These effects were not mimicked by D_1 and D_2 antagonists, and not diminished by destruction of DA systems with 6-OHDA. Thus clozapine actions do not seem to be mediated through dopamine systems. It remains difficult to tie down the receptor system as prefrontal cortex does, but lateral septum does not, have 5-HT receptors. But certainly it indicates a unique anatomical profile independent of dopamine systems.

Remoxipride

In the 1970s and 1980s, the continuing search for atypical drugs produced the substituted benzamides (e.g. sulpiride and remoxipride). Remoxipride has at least equal antipsychotic potency to haloperidol (Lewander *et al*, 1990). It is indeed non-cataleptogenic in rats (Ogren *et al*, 1990), and this is reflected in its low potential for extrapyramidal side-effects (Morrison *et al*, 1990).

The reason for its atypicality is difficult to understand. Substituted benzamides are selective and potent D_2 receptor blockers. Like clozapine, it was suggested that the drug might be site specific, and this may indeed be the case for remoxipride, as there is much evidence that it preferentially effects a subpopulation of mesolimbic D_2 receptors. Thus, in *ex vivo* autoradiography experiments, remoxipride preferentially displaces ^{3}H-raclopride from limbic areas (olfactory tubercle and septum) as opposed to striatal areas (Kohler *et al*, 1992). Chronic treatment with remoxipride, unlike with haloperidol, does not produce behavioural supersensitivity. (A mesolimbic specific phenomenon; Ogren *et al*, 1990). In addition, remoxipride fails to provoke D_2 receptor supersensitivity and fails to induce D_2-receptor dependent mRNA and neurotensin changes in the striatum (Kohler *et al*, 1991; Levant *et al*, 1991).

Remoxipride has very high selectivity at D_2 receptors only. *In vitro* radioligand studies show it to have modest affinity at D_2 receptors and negligible affinity for the D_1 receptor (Hall *et al*, 1986); it also has virtually no potential to bind to 5-HT_2, muscarinic or α adrenoceptors (Hall *et al*, 1986). Its profile, therefore, is very different from that of clozapine, and the two drugs must have differing mechanisms for their atypicality.

The pharmacology of remoxipride at the D_2 receptor family is of interest. Although it has reasonable affinity for the D_2 receptor (Malmberg *et al*, 1993), it has very low affinities for the other molecular members of that family, D_3 and D_4 (again unlike clozapine – Sokoloff *et al*, 1992; Van Tol *et al*, 1991, 1992). Of particular interest is the differential affinity of remoxipride for the long and short isoforms of the D_2 receptor, it having an order of magnitude higher affinity for the short form (Malmberg *et al*, 1993). Not enough is yet known about the function and distribution of the long and short form of the D_2 receptor to determine whether this confers the mesolimbic sensitivity to remoxipride, but it is clearly a possibility and, if so, may be a useful screen for atypical drugs.

The only other recognised high-affinity binding potential for remoxipride is at the sigma/phencyclidine binding site of the glutamatergic non-methyl-D-aspartate (NMDA) receptor (Hall *et al*, 1986). This may be of relevance, as there is now a glutamate hypothesis of schizophrenia (Meldrum & Kerwin, 1987) which is partly based on the psychotomimetic potential of agents stimulating this site (e.g. phencyclidine). Behavioural studies also show that remoxipride blocks phenylclidine-induced locomotion at theoretical antipsychotic doses (Ogren & Goldstein, 1993). However, the sigma site can also be associated with sites distinct from the combined sigma/phencyclidine site of the NMDA receptor. Therefore, further clarification is required.

Studies of c-fos expression have also been performed for remoxipride (Deutch *et al*, 1992). Remoxipride, like clozapine, does not activate the dorsolateral striatum, but activates the ventral striatum; however, unlike clozapine, it does not seem

to activate medial prefrontal cortex or lateral septum. To date there have been no functional neuroimaging studies with remoxipride detailing D_2 occupancy in patients.

Thus, whereas clozapine is a relatively non-specific, non-selective drug (and for which there are several possibilities for its being atypical), remoxipride is highly selective to D_2 receptors, and its atypicality may indeed be due to its superselectivity at subtypes of D_2 receptors, possibly the D_2b (short form) of this receptor, localised within different subsets of neuronal systems.

Risperidone

Risperidone is the most recently introduced atypical, having been launched in the UK in the summer of 1993. Risperidone is again truly non-cataleptogenic (Janssen *et al*, 1988) with clear clinical efficacy for both positive and negative symptoms. Its atypicality is not fully translated into clinical practice, as troublesome dystonias and akathisias have been described, but the drug does have a low propensity to produce Parkinsonism (Janssen Research Foundation, 1988).

Risperidone is different again from clozapine or remoxipride, as it possesses high affinity and non-selective receptor actions. Radioligand studies *in vitro* show it to have high affinity for 5-HT_2 α adrenergic, D_2 and histaminergic sites, modest affinity at other 5-$HT_{1A,C,D}$ receptors, and negligible affinity for D_1 and sigma sites (Schotte *et al*, 1989; Leysen *et al*, 1992).

Behavioural and peripheral markers of serotonin and dopamine systems show a rather complex picture for risperidone. Its atypicality in the catalepsy test (Janssen *et al*, 1988) is obviously at odds with its high affinity for D_2 receptors. Moreover, other indices of D_2 activity, such as locomotion and food intake, are only weakly antagonised by risperidone (Janssen *et al*, 1988). There is no pharmacological explanation for this. Therefore, one of the other potent effects of risperidone must be counterbalancing the D_2 effect, producing atypicality. This leaves the question open as to whether risperidone's antipsychotic effect is at the D_2 receptor or at another site. Both *in vivo* and *in vitro* studies point to a peculiarly high affinity at 5-HT_2 receptors (Janssen *et al*, 1988) (the relevance of this has been discussed under 'Clozapine' above). This *is* translated into powerful behavioural effects, as judged by sleep/wakefulness, and electroencephalographic sleep studies over the theoretical clinical dose range (Dugovic *et al*, 1989).

Complex interactive behavioural studies of risperidone's effect on serotonin-induced changes in dopamine function, and on dopamine-induced changes on serotonin function, suggest a complex interaction with risperidone of these dual systems (Awouters *et al*, 1990). These studies are difficult to interpret, but in general they support the notion that 5-HT_2 blockade compensates for some of the consequences of D_2 blockade, particularly at higher doses. This is highly relevant to the bell-shaped clinical dose–response curve for risperidone (see below).

At present there are no c-fos studies. There has been a limited study of subclinical (1 mg) doses of 5-HT_2 and D_2 receptor occupancy in two volunteers using positron emission tomography. About 50% occupancy for both was seen at 1 mg, predicting high occupancy of both receptors in the clinical dose range (Nyberg *et al*, 1993). This high D_2 occupancy explains the extrapyramidal side-effects and akathisia with risperidone at higher doses.

Data from clinical trials

Clozapine

There are two phases to the clinical trials of clozapine for the efficacy and tolerability: the early phase, before its withdrawal; and later trials, which stimulated its renaissance. In general, early trials tended to use lower dose regimes. Clozapine was originally introduced in 1966, and open-trial data were published by Brezewski *et al* in 1969. Subsequent multicentre trials with large numbers of patients appeared from 1971 (Angst, 1979) in so-called productive and paranoid hallucinatory schizophrenia. Clozapine at 150–400 mg was as effective as high-potency neuroleptics such as chlorpromazine, and superior to low-potency neuroleptics such as levomepromazine and thioridazine (Gross *et al*, 1970).

At that time these trials noted that the drug was virtually free from extrapyramidal side-effects, but hypersalivation and hyperthermia were frequent. The excessive drowsiness noted for the drug was considered as an advantage in acute cases, and it was even recommended that 10–25 mg may be useful as a hypnotic. In 1975, 16 patients of 3200 in Finland treated with clozapine developed agranulocytosis (Amsler *et al*, 1977; Idänpään *et al*, 1977), and four out of 2900 developed agranulocytosis in Switzerland, leading to the drug's voluntary withdrawal.

The drug remained available in some parts of the world, such as Germany, Denmark and Sweden, and the clinical experience of the usefulness of the drug in these countries has been documented. In Germany, the usage of clozapine increased in the 1970s and came to be anecdotally recognised as useful in up to 70% of therapy-resistant states (Helmschen, 1989),

with the occasional dramatic improvements. In all cases, extrapyramidal side-effects were said to be diminished when patients were transferred to clozapine; over seven and a half years, relapse rates were reduced from 35% to 21% per annum, and in 50% of cases there were no relapses during treatment (Pietzker & Stahl, 1988).

In Sweden, a cohort of patients in Uppsala was monitored from 1974 to 1978 (Lindstrom, 1988). This study showed a 36% drop-out rate due to lack of efficacy, intolerability, and poor compliance. Of the remainder, 36% were moderately improved and 43% significantly improved; 39% regained employment, while 10 of the 96 patients developed neutropenias, no extrapyramidal side-effects occurred.

In Denmark, the drug was relaunched in 1983, and a long-term retrospective analysis (Povlsen *et al*, 1985) showed that 51% of patients improved on being transferred to clozapine, 47% did not, and 2% grew worse. Again, occasional so-called 'special clozapine responders' were noted, and it was anecdotally noted that young adults with early-onset illness usually fell into this category.

These studies led to pressure in the USA for its reintroduction, and a series of carefully conducted trials was performed. Claghorn *et al* (1987) randomised 151 patients, who had experienced extrapyramidal side-effects on at least two neuroleptics, to either clozapine or chlorpromazine. Eleven patients on chlorpromazine continued to find the extrapyramidal side-effects intolerable, and only one clozapine patient experienced this. Scores on the Clinical Global Impression (CGI) scale and the Brief Psychiatric Rating Scale (BPRS) showed clozapine to be superior to chlorpromazine, with hardly any extrapyramidal side-effects. Hypersalivation and sedation were the main adverse effects. Kane *et al* (1988) took 319 patients refractory to three periods of 1 g chlorpromazine equivalents of two types of neuroleptic and entered them into a trial of 60 mg haloperidol: 2% responded, and of the remainder, 268 entered a trial of chlorpromazine versus clozapine. Of these, 38% of clozapine-treated patients compared with 5% of chlorpromazine-treated patients responded, with greater than 20% improvement in BPRS scores. The main adverse effects were drowsiness, salivation and fever.

Clozapine was reintroduced in January 1990 in the UK and USA, with strict haematological monitoring, for treatment-resistance or treatment-intolerant patients. Usage in general psychiatric practice suggests that one-third of patients improve dramatically; one-third derive significant benefit; and one-third do not respond (King & Mills, 1993).

Remoxipride

Remoxipride was introduced in the UK in 1989. The majority of clinical trials before its introduction were against haloperidol in acute or acutely relapsed patients. The aggregate data are well summarised by Lewander *et al* (1990). Six hundred and sixty-six patients received remoxipride, and 437 received haloperidol. At daily doses of 150–600 mg, remoxipride had similar effects to 5–45 mg haloperidol, but with much fewer extrapyramidal side-effects. In some studies, the discontinuance rate on haloperidol was 50%.

In a study of relapse prevention, Walinder & Holm (1990) performed a six-month double-blind trial, followed by a further six-month open analysis of remoxipride versus haloperidol. This showed remoxipride to be similar to haloperidol, but with much lower rates of emergent symptoms. A study by Chouinord (1990) with placebo and chlorpromazine as comparators showed remoxipride to be superior only in those who were previous good responders to neuroleptics. The most frequent side-effects in all the trials for remoxipride were akathisia, tremor and rigidity, but at rates of 50% less than with equivalent doses of haloperidol.

Risperidone

Risperidone was introduced in 1993. There have been seven multicentre, double-blind trials against haloperidol, and single trials against clozapine, perphenazine and levomepromazine. The trials were all similar, involving a somewhat short (one-week) wash-out. Most trials involved a dose-finding protocol against a standard 20 mg dose of haloperidol, followed by a six-week constant-dose period. The short wash-out and the fixed low-dose haloperidol may be responsible for some of the idiosyncratic results, such as a worsening of the placebo group, poor responses to haloperidol, and extrapyramidal side-effects in the placebo group. Nevertheless, using the BPRS, CGI, and the Scales for the Assessment of Positive and Negative Symptoms, there were impressive results for risperidone, with low scores for extrapyramidal symptoms. There is a bell-shaped response curve for risperidone, with maximal antipsychotic efficacy at 6–10 mg, a dose which does not seem to provoke Parkinsonism, but in which there were a number of akathisias and dystonias reported. Drug-induced Parkinsonism is reported at higher doses, but these doses are therapeutically ineffective, so this scenario should not develop.

These data are largely in the form of Janssen technical reports, but a number of examples have now been published (Svestka *et al*, 1990; Claus, 1992).

In a study (unpublished technical document) of 4–8 mg risperidone and 400 mg clozapine, the two drugs were statistically indistinguishable. However, this was with a small sample size, of 20 patients, with variable dosage of respiridone compared with a fixed dose of clozapine, and it is impossible to draw firm conclusions. Longer-term studies are under way in relapse prevention.

Position statement

All new atypicals are probably at worst equi-effective as classic antipsychotics and certainly superior in their tolerability and side-effect profile, and the monitoring service for clozapine effectively neutralises the risk of adverse consequences to agranulocytosis. Using such drugs at the end of a clinical decision tree because of their novelty probably militates against their optimal usefulness. There is probably sufficient diversity of choice for them now, as a group, to replace classic antipsychotics in first onset and acute relapses from routine clinical practice. Were it not for agranulocytosis, clozapine would be the first choice. However, for this reason it is reserved to treatment-resistant or treatment-intolerant cases, and it is certainly the drug of choice here.

Patients probably should not be given prolonged treatment with classic antipsychotics before considering clozapine. Remoxipride would seem to be a sensible first choice, as it is effective and well tolerated. It is also probably an excellent choice for relapsed patients who have previously responded to classic antipsychotics and on whom one does not want to inflict extrapyramidal side-effects.

The clinical trial data on risperidone does not seem transparent enough to make firm recommendations, and so it may best be reserved as second line, since remoxipride is considerably cheaper. There are no objective data to suggest risperidone offers any advantages over remoxipride.

In treatment difficulties, clozapine probably should be considered early, as illness duration can militate against neuroleptic response in general and clozapine response in particular (Kerwin & Lofts, 1993). Because of clozapine's potential to improve social functioning, quality of life and negative symptoms, earlier use could be considered for particular patients.

There are many other areas where the relative merits of classic versus atypical antipsychotics need further clarification, for instance: in the very behaviourally disturbed patient, where sedation is a requirement; for relapse prevention; where there are compliance difficulties and depot medication is being considered; and in elderly patients.

Atypical antipsychotics, because of the initial empirical style of screening, always proved to have an unsuspected twist to their pharmacology, which opened novel avenues to schizophrenia research. Thus they have provided important clues to the neuroanatomical localisation of schizophrenia and have helped to reformulate the dopamine hypothesis of schizophrenia. Their unusual actions were the driving force behind the search for genetic subdivisions of the dopamine receptor, and their subsequent pharmacology at these receptors has reconciled some long-standing anomalies in the psychopharmacology of schizophrenia.

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