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abstract

Objectives: to evaluate the possible alternatives after failure of first-line antipsychotic treatment. **Methods:** a Pubmed search was carried out, update date 31/01/2013, with the following strategy: "Antipsychotic Agents" OR "Schizophrenia/drug therapy" OR "Psychotic Disorders/drug therapy" AND "switching", "treatment-resistant", "monotherapy", "Polypharmacy", "Drug Therapy, Combination", "Delayed-Action Preparations", "Dose-Response Relationship, Drug", "Polypharmacy". **Results and conclusions:** Before opting for pharmacological management for patients with schizophrenia, psychotherapy and the prescription of physical exercise should be considered. If there is no improvement then medication could be indicated. When the initial medication fails, the first step would be to increase the medication up to the maximum dose; if not effective, the drug could be replaced by another antipsychotic agent, and if this fails, then clozapine should be considered. In cases of adherence problems, it may be useful to employ intramuscular administration of long-acting antipsychotic drugs. The combination of two or more antipsychotic drugs is not recommended in any case.

Antipsychotic therapy after failure with first-line treatment: should we increase the dose, switch drugs, or combine antipsychotics?

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Introduction

Schizophrenia is a complex disorder in which up to one third of the patients do not respond satisfactorily to antipsychotic therapy and where complete recovery is an exception.[1] The functional status of these persons is considerably altered, especially in relation to negative symptoms (affective flattening, anhedonia, apathy), emotion-related symptoms (dysphonia, depression-like symptoms, autolytic ideation) and cognitive-related symptoms (attention, memory, cognitive symptoms). The majority of the negative symptoms are secondary to pharmacological treatment.

In the 1950s *First Generation Antipsychotics* (FGA) were developed. Potency was related to adverse effects, that is, those more incisive antipsychotics, produced greater dopaminergic blockade and therefore greater extrapiramidal symptoms.

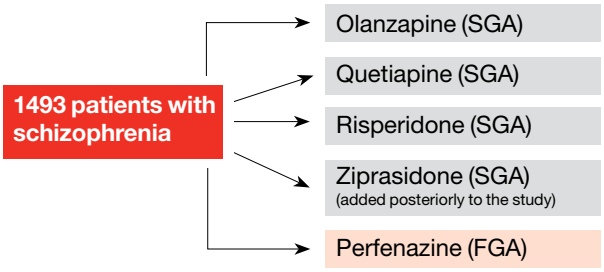
From the 1980s, atypical antipsychotic agents or *Second Generation Antipsycotics* (SGA), were developed and are characterised by a low afinity for D2 dopaminergic receptors, and a high affinity for other neuroreceptors in particular 5-HT2A. These drugs appeared to have important advantages in comparison to their predecessors, including greater efficacy in positive, negative and emotional symptoms, and better tolerance. Their elevated cost supposedly was compensated by a reduction in the use of health services, given the clinical stability of the patients. Despite these affirmations, numerous meta-analyses, and systematic reviews have offered evidence showing limited superiority of the SGA.[2]

Comparative Effectiveness of First and Second Generation Antipsychotics

For years, the use of atypical antipsychotic agents for the first episode of schizophrenia was a common recommedation in the majority of guidelines and algorithms dedicated to the management of the disease (American Psychiatric Association <APA> Schizophrenia Treatment Guideline, Expert Consensus Guideline on Treatment of Schizophrenia, Texas Algorithm Project <TMAP> Schizophrenia Algorithm, Schizophrenia Patient Outcomes Research Team <PORT>, International Psychopharmacology Algorithm Project, Schizophrenia Algorithm, National Institute for Health and Clinical Excellence <NICE>)[3,4]. However, this recommendation was contrary to the scientific evidence offered by studies which will be outlined below.

Clinical Antipsychotic Trial of Intervention Effectiveness (CATIE)

This is a double-blind randomized trial carried out in the USA.[5,6] The primary endpoint was **time to discontinuation or change to another antipsychotic drug due to any other cause** (lack of efficacy, side effects or patient's choice). The trial was carried out in 57 centres from 2001 to 2004 and participants were generally stable, with an average duration of the disease and history of treatment of about 14 years. Study design:



The results showed that all the drugs presented limitations and up to 74% of the patients discontinued treatment during the 18-month period of study. The average time to discontinuation was 4.6 months.

Olanzapine presented the lowest rate of discontinuation, but also showed the highest rate of adverse effects. Surprisingly there were no differences among the rest of the SGAs or in the case of perfenazine in terms of effectiveness or extrapiramidal effects. There was no evidence that SGAs were better for negative symptoms of cognitive deficits. Each drug though, presented specific side effects. Olanzapine caused the greatest weight increase and dyslipidemia; quetiapine, the highest rate of anticholinergic effects; risperdone, hyperprolactinemia and greater side effects related to sexual function.[2]

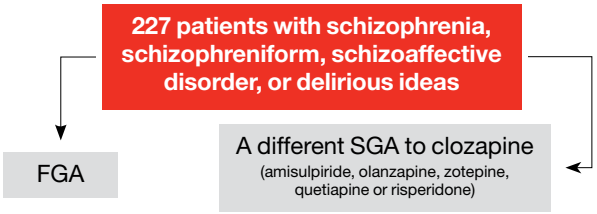
One of the multiple criticisms of this study is related to the active comparators chosen. Perfenazine is a FGA of medium potency producing mild extrapiramidal effects, which compared to a SGA, it is expected to show a slightly lower efficacy and a similar incidence of extrapiramidal effects. If another FGA had been chosen as a comparator to SGAs, then the results would have been different. Moreover, when employing time to discontinuation as the primary endpoint, an adequate evaluation of the complex trajectory of patient response to the new treatment cannot be made.[8]

The different characteristics of the drugs, patients and clinicians can lead to variations in relation to the decision to discontinue treatment. For example, sedation or acathisia can produce an earlier discontinuation while weight gain or laboratory changes can lead to the decision of discontinuing treatment at a later date.[9] Moreover, the modifications in treatment in phase 1 of the study could reduce some symptoms, which could lead to a greater desire by the patient to change treatment. On the other hand, omitting the recording of the reason for discontinuation when the decision is considered as "the patient's choice", makes it impossible to be classified as a discontinuation due to intolerance, when in reality there may be a possibility that this would be the case.[8]

Another factor that could influence the result of the study, is the drug dose employed, given that even the authors recognized that quetiapine, risperidone and ziprasidone doses could not have been optimum.[9] Therefore this trial was biased in favour of olanzapine with respect to FGAs and the rest of SGA evaluated.

Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS 1)

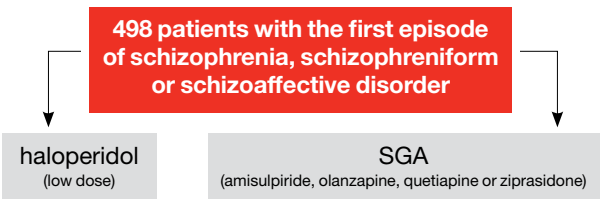
This is a randomized open trial carried out in the United Kingdom.[7] Study design:



In general, the results did not show an advantage to SGAs in terms of quality of life (primary endpoint) or the improvement of symptoms in one year (secondary endpoint). There were no differences in the rates of extrapiramidal effects evaluated objectively.[2]

European First Episode Schizophrenia Trial (EUFEST)

This trial lasted one year and was carried out in various European countries. The aim of the trial was to evaluate the comparative effectiveness in terms of **time to discontinuation due to any cause** (considered as a compendium of efficacy and safety or drug tolerance). The study design was as follows:



First and Second Generation Antipsychotics have similar efficacy and tolerability

It was observed that, in patients with the first psychotic episode, time to discontinuation was significantly greater in patients receiving low-dose haloperidol than in those under SGAs, where olanzapine was the drug with the least rate of discontinuation. However, the reduction of symptoms was virtually the same in all groups. Therefore, it cannot be concluded that the SGAs are more effective than haloperidol, given the lower rates of discontinuation that are not necessarily associated to improvement in symptoms.[10]

Relapse prevention (Kishimoto y cols)

There are few controlled trials that have compared FGAs to SGAs in relation to the relapse prevention in schizophrenia. A systematic review and meta-analysis of randomized trials lasting six months or more was carried out to compare both types of antipyschotic drugs. The primary endpoint was relapse. The secondary endpoints included relapse after 3, 6 and 12 months, treatment failure, admission to hospital, discontinuation due to any cause and lack of adherence and tolerance. A total of 23 studies were included with 4504 participants overall.

In this review it was found that, while in some individual studies the SGAs were associated with isolated and significantly lower relapse rates, these findings were not corroborated after the authors released individual-patient data from three trials in order to carry out the meta-analysis. The exception was with risperidone, that showed significant superiority over FGAs after 3 and 6 months.

The SGAs showed slightly higher efficacy when compared to FGAs in relapse prevention. This was confirmed in double-blind studies, in patients with a first episode or multiple episodes, and in comparison with different equivalent doses of haloperidol. The relevance of this superiority of the SGAs compared to FGAs in different aspects depends on whether the SGAs conform to a homogenous group and on whether low to moderate potency FGAs are chosen as comparators instead of haloperidol.

Thereby treatment should be prescribed according to the patient's characteristics and the particular drug factors should be taken into account.[11]

Long-acting Second Generation injectable Antipsychotics did not prove to be better than long-acting First Generation injectable Antipsychotics

Other studies

A review and meta-analysis of randomized clinical trials was carried out to compare the efficacy and tolerance of FGAs and SGAs in patients with treatment-resistant schizophrenia.[12] Twelve controlled studies were identified (1916 patients overall). A meta-analysis including 7 studies comparing clozapine with FGAs was performed to assess the effects of this drug on psychopathological aspects, response rates, extrapiramidal effects, and late dyskinesia. The results showed that SGAs were superior in terms of adherence and lower rates of extrapiramidal effects when compared to FGAs were observed. However, and with the exception of clozapine, their efficacy in the reduction of symptoms of treatment-resistant schizophrenia has not been established.

A meta-analysis of randomised controlled trials compared the effects of FGAs and SGAs.[13] A comparison of 9 SGAs with FGAs was made on efficacy in general (primary endpoint), including positive, negative and depression-related symptoms, quality of life, extrapiramidal effects, weight gain, and sedation. A total of 150 double-blind trials were included, the majority short term, with 21,533 participants overall. Four of the SGAs proved better than FGAs in efficacy in general (amisulpiride, clozapine, olanzapine and risperidone). The rest of the SGAs were not more effective than FGAs, not even in the case of negative symptoms. The SGAs induced less secondary extrapiramidal effects than haloperidol (even at low doses). Except for aripiprazole and ziprasidone, all SGAs produced higher weight gain compared to haloperidol, but not as much as low potency FGAs. The SGAs also differed in sedative properties.

In general, the new SGAs have not proven to be more effective or better tolerated than the older FGAs.

What should we do if a patient does not respond to first-line antipsychotic treatment?

The first step to be carried out in the case of a patient not responding adequately to first-line pharmacological treatment is to review the patient's diagnosis, verify objectively whether there was adequate adherence to treatment (at right doses and treatment length) and consider other causes that could influence treatment outcome such as drug abuse, concomittant use of other medication, and the existence of other medical illnesses that could interfere in that response.[1,4]

Should we increase the dose of antipsychotic drugs?

When there is a lack of response to antipsychotic treatment at full therapeutic dose, one of the common options employed by clinicians is to increase the dose even further.

There is no evidence that the prescription of higher doses than the maximum recommended dose is more effective. The main guidelines have consistently recommended the use of standard doses in routine clinical practice, excluding this recommendation for a small group of patients in which a rapid metabolic rate of the drug has been determined.[1]

Switching to a different antipsychotic?

Another option when facing partial efficacy or no response to first-line antipsychotic treatment is switching the drug. Various above-mentioned studies offer data in relation to patients follow-up or after treatment change or discontinuation of the first drug.

Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE)

After phase I of the CATIE trial, further studies were performed that also generated interesting results. The trial's design was as follows:

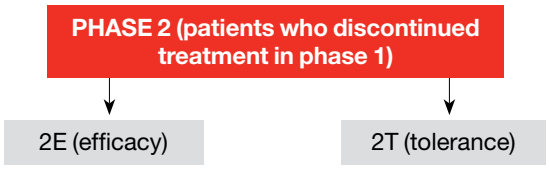
PHASE 1A: patients that were excluded from perfenazine in phase 1 due to tardive dyskinesia

PHASE 1B: patients that discontinued perfenazine in phase 1

→ Olanzapine
→ Quetiapine
→ Risperidone

The time to discontinuation (primary outcome) was longer for patients under quetiapine and olanzapine than those under risperidone. There were no significant differences between treatments in relation to discontinuation due to inefficacy, intolerance or patient's choice.[14]

Patients who discontinued treatment in phase 1 were offered the possibility to participate in phase 2. They could choose between two random paths, 2E and 2T, with the help of therapists and doctors. See figure below.



The major difference between the sample of patients in phase 1 and phase 2 was that patients who discontinued treatment in phase 1 on their own probably did not reach an agreement or understanding with their therapist and the majority of them logically did not participate in phase 2.

The pathway to efficacy (2E) was recommended to individuals who discontinued previous treatment due to inefficacy. Clozapine (open) was compared to double-blind treatment with either, olanzapine, quetiapine or risperidone.[9] In this case, clozapine proved more effective than the other SGAs, with an average period of discontinuation of 10 months, doubling the duration of the next, which was olanzapine.[2]

The pathway of tolerance (2T) was recommended to those individuals who discontinued treatment in phase 1 due to intolerance. Double-blind treatment was compared with olanzapine, quetiapine, risperidone and ziprasidone. The time to discontinuation (primary outcome) was longer in patients under risperidone and olanzapine compared to quetiapine and ziprasidone. In the 2T pathway, there was a higher proportion of patients that did not tolerate the treatment assigned in the first phase. However, the results in this phase showed that olanzapine was the most effective for those who discontinued treatment due to inefficacy, but not due to intolerance or any other reasons. Risperidone was equally effective among patients who discontinued treatment due to inefficacy or lack of tolerance. [9]

In a sub-analysis of the CATIE trial, the authors examined the findings of phase 1 to evaluate whether it was more advantageous to continue treatment under the same drug they were taking when recruited for the study or to switch the drug altogether. For those individuals randomly assigned to either olanzapine or risperidone who continued with the same treatment, higher time to discontinuation rates were observed versus switchers.

This evidence suggests that switching antipsychotics has its limitations in terms of success as a strategy. Unless the clinical situation requires it, the physician (along with the patient and always respecting the patients desire to change treatment) should strive to optimize the prescribed drug regimen by carrying out changes in the administration route, psycho-social and behaviourial interventions or, at precise moments, offering adjunct non-psychotic therapy before making modifications in treatment.

Changing treatment offers the possibility of improving the symptoms or reducing the adverse effects produced by a specific antipsychotic agent. Nevertheless, a change in medication can increase the risk of psycopathological descompensation in a stable patient and increase workload pressure on health services and consume more resources.[15]

Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS 2)

The CUtLASS 2 trial compared different SGAs in 136 patients who did not respond well to two or more drugs employed previously. A significant advantage was observed in the case of clozapine in the improvement of symptoms after one year and furthermore, the patients showed a significant preference for it.

In both the CATIE and the CUtLASS studies, clozapine proved to be a valid alternative when other drugs had failed, an issue we will address later.

Impact of the administration route on treatment efficacy.

Another possibility of modifying treatment is to employ a long-acting injectable antipsychotic, which could increase adherence to treatment rates, lead to clinical improvement, and incur lower health costs for patients with schizophrenia. There are various options, of which it is worth mentioning, zuclopenthixol deconoate (FGA), fluphenazine deconoate (FGA), pipothiazine palmitate (FGA), long lasting injectable risperidone (SGA) olanzapine pamoate (SGA) and paliperidone palmitate (SGA).

Currently there is no evidence that the long-acting injectable SGAs are better than long-acting injectable FGAs. In Spain, the most efficient option is fluphenazine.

Time to prescribe treatment change

Another important question that arises on addressing this issue is the time period of treatment with a drug before considering a change to another drug due to inefficacy. There is no evidence-based answer and there is great variation between different institutions where treatment is given and differences among psychiatrists.[16]

Before deciding on pharmacological management of schizophrenia, it is recommended to consider specific psychosocial interventions

Factors associated with change

A trial[17] studied the factors associated with the change from FGAs to SGAs or to antipsychotic polypharmacy. An evaluation of the evolution of disease in relation to the mental status and social functioning of patients was carried out.

It was observed that those patients who had modified treatment from a FGA to a SGA presented lower rates of admission to the psychiatric ward than before, a lower duration of illness, lower rates of substance abuse and a higher probability of working in competitive scenario. However, they did present more pronounced symptoms of disease than those who continued with FGA. The mental status and social function was more favourable for those who changed to a SGA in monotherapy, but not for those taking FGA and SGA concurrently. Another observation of this study was that the strategic approach strongly depended on the practices of the institution, in addition to the course of the disease and the use of health services.

Change to clozapine

One of the most common recommendations found in management guidelines and algorithms for schizophrenia is the use of clozapine after one or two failed attempts with other antipsychotics.[3]

Clozapine was the first SGA developed. In 1977, a 2% risk of agranulocytosis was decribed in relation to its use, and clozapine was withdrawn from the market. However, it was commercialized again under a new dose (with a single indication for the treatment of refractory schizophrenia). This drug is subject to a strict protocol with close hematological monitoring and caution for side effects.

The first study showing efficacy of clozapine in refractory schizophrenia was performed in 1988. A trial was carried out in patients not responding to haloperidol and individuals were randomly assigned to clozapine (900 mg/d) or clorpromazine (up to 1800 mg/d). It was observed that there was a 30% therapeutic response in the case of clozapine in comparison to 4% with clorpromazine.[18]

Later it was demonstrated that clozapine is more effective than FGAs in the treatment of schizophrenia[19] and mainly in those patients who did not respond adequately to other FGAs. Clozapine also proved more effective than other SGAs in the management of patients with inadequate response to FGAs. In addition, favourable results with this drug were also found in comparison to other SGAs, just as was described previously in studies such as the CATIE, CUtLASS and other meta-analyses.[3]

Despite the evidence described, data on prescription in clinical practice indicate that the use of clozapine is much lower than expected according to the incidence of refractory schizophrenia. This could be related to the need for hematologic monitoring, the high frequency of physician visits, adverse effects (agranulocytosis, weight gain, hyperlipidemia, and an increase in the risk of diabetes), in addition to the lack of experience with clozapine on the part of health professionals given the above-mentioned risk factors.[3]

Some studies have attempted to demonstrate the efficacy of adding a second antipsychotic to patients who have responded partially to treatment with clozapine. However, the evidence supporting this clinical practice is weak[20-26] and the benefits observed are either modest or absent.

Combine antipsychotics?

Another common recommendation of the majority of the treatment guidelines for schizophrenia is not to employ combinations of antipsychotic agents or employ them only as a last resource.[3] This option can be considered only after having employed at least two antipsychotic agents with different mechanisms or tolerance characteristics, at the maximum dose and for an adequate period of time, and after verifiying clozapine failure.[27]

In case of opting for this approach, it should be carried out in the context of an individual trial for each patient, with close monitoring of clinical response, adverse effects and the physical health status.[28] Despite the lack of evidence, there are numerous studies that show that antipsychotics are combined frequently.[29] Table 1 shows the main studies that have evaluated the combination of antipsychotics.

The Canadian Agency for Drugs and Technologies in Health (CADTH) has published a systematic review on the combination and use of high doses of antipsychotics in schizophrenic patients. The main recommendations are[36]:

· In the case of patients not responding to habitual doses of clozapine in monotherapy, combinations of antipsychotics should not be used where clozapine forms part of the combination.
· In patients who do not respond to the habitual doses of an atypical antipsychotic, it is not recommended to employ combinations of atypical antipsychotics.
· Clozapine is recommmended at standard doses in patients with schizophrenia who do not respond to adequate doses of an atypical antipsychotic agent.
· In patients with schizophrenia who do not respond adequately to habitual doses of atypical antipsychotics, it is not recommended to prescribe high doses of atypical antipsychotics.

Can we combine other drugs to antipsychotics?

If no response to schizophrenia treatment, another strategy employed by numerous psychiatrists is combining other drugs to potentiate their effects (lithium, anticonvulsivants, etc.). However this cannot be considered as a first option when deciding on a change of strategy in management, but a reserved choice for specific cases.

Alternative and support therapies?

On the other hand, table 2 shows a profile of the use of antipsychotics in monotherapy compared to combined therapy. In 2012, approximately 9700 patients were treated with antipsychotics in Navarre (1.6% of the total population). Of these, 87% were under monotherapy, which adjusts quite well to the current recommendations.

Data on the use of antipsychotics in Navarre, Spain

According to the data on consumption of antipsychotics in Navarre, it is observed that between 2000 and 2011 their use has doubled. It should be pointed out that these data are a reflection of global consumption, which includes schizophrenia and other indications. The use of SGAs has clearly increased with respect to FGAs. This tendency is not based on scientific evidence given that, as shown in this article, there are no clear advantages of SGAs over FGAs (figure 1).

On the other hand, table 2 shows a profile of the use of antipsychotics in monotherapy compared to combined therapy. In 2012, approximately 9700 patients were treated with antipsychotics in Navarre (1.6% of the total population). Of these, 87% were under monotherapy, which adjusts quite well to the current recommendations.

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Conclusions

Before deciding on pharmacological management of schizophrenia, it is recommended to consider specific psychosocial interventions.

If there is no improvement, then pharmacological treatment should be considered.

Before defining failure of pharmacological therapy the dose should be increased to maximum therapeutical doses; if not effective, switch to another antipsychotic, and if this approach also fails, then consider prescribing clozapine.

In case of adherence problems, an intramuscular long-acting injectable antipsychotic should be considered.

Monotherapy is recommended, as combined therapy does not improve efficacy and increases the risk of drug safety problems.

There is no available evidence to support the chronic use of antipsychotic agents in all schizophrenic patients.

Table 1: Studies evaluating the combination of antipsychotics.

AUTHORS	OBJECTIVES	DESIGN / RESULTS	CONCLUSIONS / COMMENTS
Barbui and cols	Establish whether excess doses and/or antipsychotic polypharmacy is associated with elevated levels of psychopathology. Establish whether the use of SGAs is either a protecting or risk factor in these strategies.	375 patients followed up for one year. 28% excessive dose. 13% polypharmacy. Multivariate analysis: psychopathology was not a predicitive factor. Use of SGAs not associated with polypharmacy and excessive dose.	High antipsychotic doses due to concurrent use of FGAs and SGAs at the beginning of the study.[30]
Pandurangi and cols	Evaluate the prevalence of polypharmacy with SGA. Pharmacological reasons for this strategy. Evidence in favour or against this approach.	Review. Polypharmacy with antipsychotics not rare Prevalence 3.9-50%. Randomized, blinded controlled trials were scarce.	The effects of the combination of SGAs should be investigated in schizophrenic patients with treatment resistance or presenting intolerable adverse effects.[31]
Correll and cols	Evaluate the therapeutic and adverse effects of antipsychotic polypharmacy compared to monotherapy in schizophrenia.	Meta-analysis. 19 studies. 1,229 patients. In some circumstances, polypharmacy was superior to monotherapy.	Possible publication bias. Need for future investigations.[32]
Suzuki and cols	Effectiveness of switching from polypharmacy to monotherapy.	Case series. 25 chronic patients with antipsychotic polypharmacy at high doses with no improvement. Change to a SGA in monotherapy.	It is suggested to employ SGAs in monotherapy even for patients previously taking combinations of antipsychotic agents (polypharmacy) in vain.[33]
Suzuki and cols	Efectiveness of switching from polypharmacy to monotherapy.	Patients previously treated with an average of 3 antipsychotic agents maintained for more than 6 months. Evaluation of 44 patients under monotherapy. 54.4% were stable. 22.7% improved 22.7% worsened.	In many cases polypharmacy with antipsychotics was avoidable.[34]
Essock and cols	Risks and benefits of maintaining polypharmacy or switching to monotherapy.	Randomized trial. 127 patients with schizophrenia under treatment with 2 antipsychotics. Randomized to maintain polypharmacy or change to monotherapy. Monotherapy: shorter discontinuation periods. Weight reduction Continuation in polypharmacy: weight increase. No differences in terms of psychiatric symptoms and hospital admissions.	The authors supported the need for adequate trials with monotherapy for individuals receiving a combination of antipsychotics under polypharmacy.[35]

Figure 1. Evolution of consumption in DDD of antipsychotic agents in Navarre between 2000-2011.

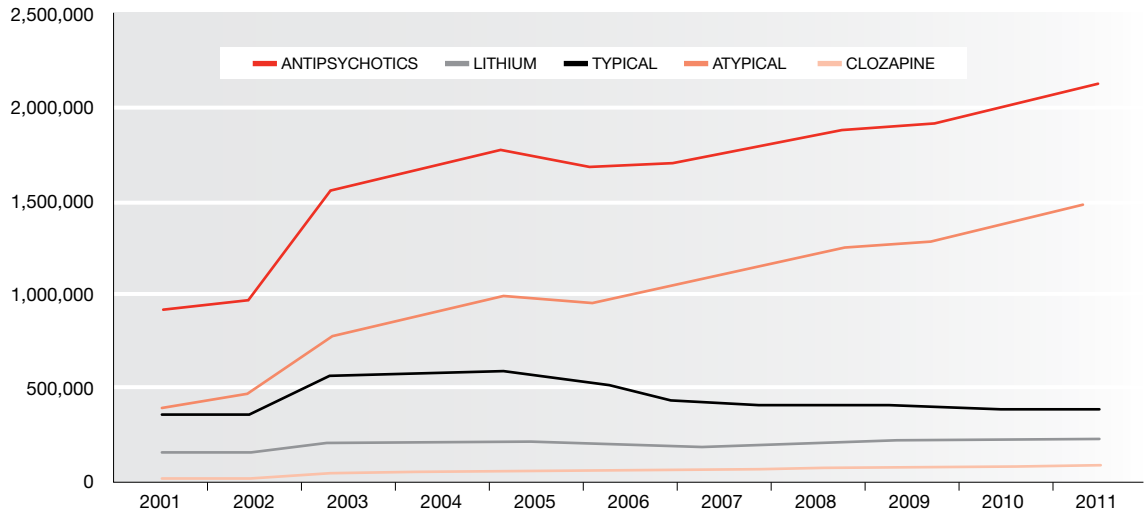

Table 2. Number of antipsychotics per patient. Year 2012.

No ANTIPSYCHOTICS PER PATIENT	PATIENTS	%
1	8,449	87.1%
2	1,060	10.9%
3	169	1.7%
4	22	0.2%
5	2	0.0%
7	1	0.0%
Total	**9,703**	**100.0%**

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