Psychiatria Danubina, 2014; Vol. 26, Suppl. 1, pp 19–22 *Conference paper*

TITLE MAXIMIZING SALES OF ATYPICAL ANTIPSYCHOTIC DRUGS

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SUMMARY

Background: *A pharmaceutical firm that has an antidepressant is a happy one for 1/5 of the population is likely to consume it. A pharmaceutical firm that has an antipsychotic is less happy since the prevalence of schizophrenic and other psychotic disorders is stable, and averages around only 1-2%. However, between 1997 and 2007, the daily consumption of neuroleptic drugs has increased by 14% in Belgium! Whatcommunication strategies have been implemented to promote their sales?*

Method: *Four messages have been identified and examined: 1) These disorders are serious and require the systematic prescription of neuroleptics; 2) These are chronic disorders for which we must consider lifelong treatment, preferably as"deposit"; 3) schizophrenia, in particular, has a peak prevalence at 18: Young people should be monitored; 4) There are means of early detection of at-risk youth that must be addressed at this stage with neuroleptics.*

Results: *1) YES these disorders are serious and require the prescription of neuroleptics, HOWEVER 2) At least 40% of patients do NOT display a chronic evolution and the "deposit" forms should be reserved for certain situations; 3) YES, schizophrenia has a peak prevalence at 18, and young people must be monitored, However 4) Our ability to achieve pre-diagnosis is limited. If prescribing neuroleptic drugs to all at-risk youth might prevent the onset of the disorders, it would also result in prescribing them to some persons who do not need them two out of five times.*

Conclusions: *from these four arguments, only one is valid whereas the remaining three are only partially valid; nevertheless, since the advent of second generation antipsychotic drugs, their consumption has increased by 14% in 10 years.*

Key words: *antipsychotic drugs - neuroleptics - atypical - schizophrenia*

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BACKGROUND

The two major areas in which psychiatry claims to provide a treatment are those of depression with antidepressants and of psychotic disorders with antipsychotic drugs (or neuroleptics). If the 90s were the years of SSRIs, the 2000s were those of the 2nd generation neuroleptics. History will judge the truly innovative nature of these molecules (Zdanowicz et al. 2008). They have at least brought some flexibility to their use because the side effects due to the atypical neuroleptic drugs are less disabling than those associated with the previous generation neuroleptic drugs. What is certain is that these molecules have highlighted the sagacity of pharmaceutical companies in increasing their sales. Today, a pharmaceutical firm with an antidepressant is a successful company because one fifth of the Western population will be suffering from a depressive episode in their life, and in 2020, depression will be the 2nd leading cause of disability worldwide. A firm which possesses an antipsychotic drug is less fortunate because the prevalence of psychotic disorders averages only 1 to 2%. How then can it increase its sales? In terms of the prescribed doses per day in Belgium between 1997 and 2007 (Zdanowicz et al. 2010), we observe a raise of 14% in the prescription of all neuroleptic drugs combined, whereas there were obviously no more psychotic patients in 2007 than in 1997 (data: National Institute of Statistics)! Various arguments have been put forward in the 2000s in order to increase sales (Figure 1).

METHOD

Four messages focused on schizophrenia and psychoses spread by pharmaceutical companies during the 2000s have caught our attention:

1) These disorders are serious and require the systematic prescription of neuroleptics;
2) These are chronic disorders for which we must have lifelong treatment, preferably as"deposit";
3) Schizophrenia, in particular, has a peak prevalence at 18: Young people should be monitored;
4) There are means of early detection of at-risk youth that must be addressed at this stage with neuroleptics.

In the late 2000s, a fifth strategic message was spread according to which neuroleptics are also useful for other disorders than schizophrenia and psychoses. From that moment on, pharmaceutical firms no longer spoke of "antipsychotic" but of "neuroleptic" drugs. This "requalification" allows to better position the molecules in other indications. Not to mention bipolar disorder (for which the first-generation neuroleptics were already used) now, their indication includes depression, anxiety disorders, and borderline disorder. Neuroleptics have thus become the panacea of Psychiatry. As it is, not, strictly speaking, a message on schizophrenia and psychoses, we will not consider this point.We will focus on the first four messages and examine their reliability, not only in the light of text books but also of recent publications (Pubmed, Medline, PsycARTICLES, PsycINFO).

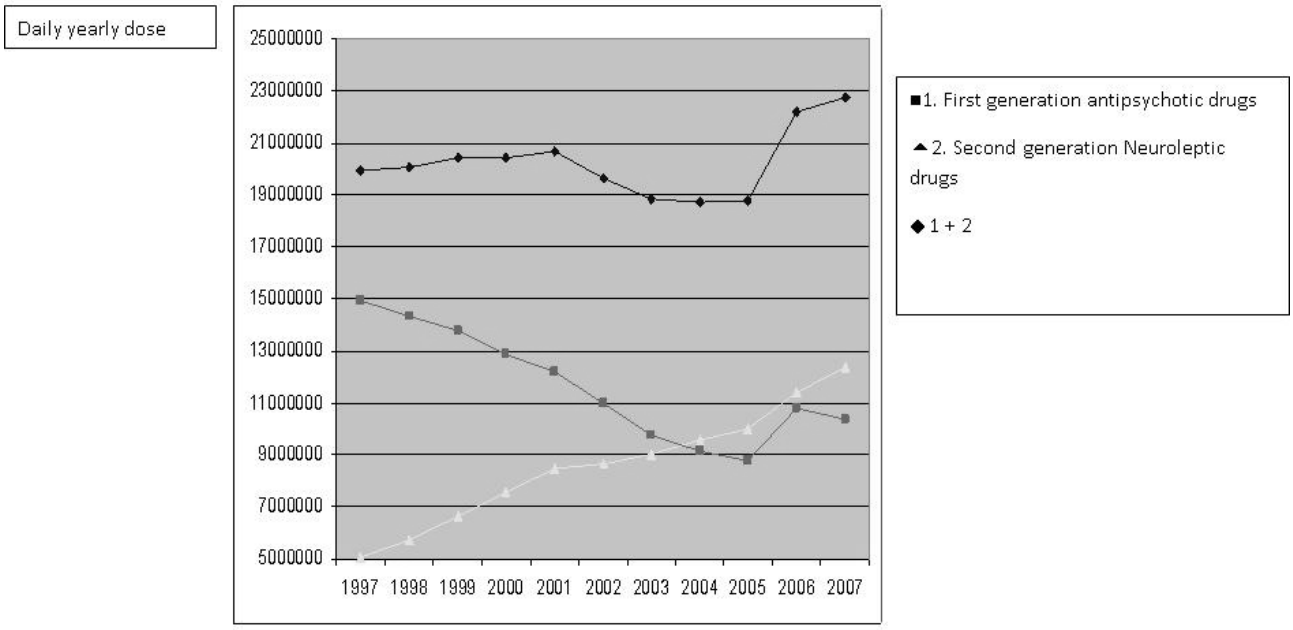

Figure 1. Daily dose of antipsychotic drugs per year / year sold in Belgium

RESULTS

Epidemiology, diagnosis and severity factors

The prevalence of schizophrenic disorders is relatively low below 12, and has a peak prevalence between 15 and 18. Beyond 18, the peak disappears and the prevalence of the disorder in the general population averages 1%. The onset of new cases older than 45, is rare. In Belgium, there are 2.5 patients suffering from psychosis per 1000 inhabitants, which represents medical costs of some € 310 million per year (Zdanowicz et al. 2006). Globally, psychoses represent the 8th leading cause of disability in the 15-44 cohort. The disorder affects twice as males as females. There are also differences in prevalence by socio-cultural milieu. Globally, 1/4 of patients who have had a psychotic episode will never relapse; 1/4 will have several attacks and then recover; 1/4 will have several attacks and then enter a chronic condition, and finally, 1/4 will enter a chronic condition from the onset (Zdanowicz et al. 2002). This global prognosis varies depending on the type of psychosis (schizophrenia having the worst prognosis), the age of onset (the earlier the onset the worse the prognosis), the level of adaptation before the first episode, and the level of recovery that follows, the number of crisis, family history... It is also obvious that if a clear factor that can be treated is involved in the genesis of the disorder, the prognosis is better. Examples of such factors are a specific stress, the use of narcotics, a very pathological communication style in the family... One important prognostic element, especially for schizophrenia, is the mode of development of the disease: acute or insidious. The acute nature of the disorder allows easier diagnosis and offers a better prognosis. For one teenager in two, the beginning of the disorder is progressive and insidious.In these forms of schizophrenia with insidious onset, the negative symptoms precede the positive symptoms which will increase with age. This form of insidious schizophrenia is correlated with a pessimistic diagnosis for at least 3/4 of the adolescents affected by it as compared with the acute form whose long term diagnosis is optimistic for more than 60% of the cases.

Early diagnosis

Given the poor prognosis, especially for young people with an insidious onset, the idea of finding a way to make an early diagnosis has soon emerged.Two avenues were explored: that of at risk personality characteristics,and that of the detection of the insidious symptoms (Zdanowiczet al. 2002). These two tracks partially overlap because some insidious symptoms are included in the description of personalities at risk. The three main at risk personality types that have been described are the paranoid, the schizotypal and schizoid (or schizotypal) personality types. The paranoid personality type proved to be the leastdisappointing as a predictor. Although it evolves more easily to paranoid schizophrenia, this is true in less than 15% of the cases. The schizotypal personality is presented as a general model of deficit in social and interpersonal relationships experienced with feelings of discomfort. Individuals presenting these personality characteristics have limited capacity to develop close relationships because of the originality of their thought processes, appearance and behaviour. Not only do they have difficulties reaching out to others, but in addition, they are rejected because they are considered"too weird." From the epidemiological point of view, the prevalence of this personality type is around 3%. The disorder is more common in foreign environments, also more common in families where there are schizophrenic or schizotypal members

and more men than women are affected by it. Rarely and especially under intense stress, do these patients react with frank psychotic disorders. These decompensations are short and associated with a good prognosis. Overall, the mental health prospect of these people is determined by other motives of treatment such as anxiety and depression. Schizoid personality is a general mode of indifference to social relationships with restricted emotional capacities. It is considered more abnormal than schizotypal personality. From the epidemiological point of view, its exact prevalence is unknown because it is rare. It would be more frequent in recent immigration populations and in families in whom some members are affected with schizophrenia or with a schizoid personality. These people decompensate mainly with depression and rarely with delusional schizophrenic episodes. Using these personality disorders as a means of early detection is problematic for at least two major reasons. On the one hand, it is theoretically "forbidden" to make a diagnosis of personality disorder in adolescents, and secondly the evolution of a psychotic disorder from a personality disorder is far from the rule because itoccurs in a small percentage of cases. Researchers have therefore turned to the 2nd track based on the detection of insidious symptoms. The insidious symptoms that were initially identified are the "negative" symptoms of schizophrenia. However, compared to "normal" adolescent behaviour, these negative symptoms were not prominent enough. Despite these difficulties, since the advent of atypical neuroleptics, the 2nd track enjoys great success.It gave birth to a new typology: the ultra high risk (UHR) category whose inclusion in the DSM5 has been discussed.

The Ultra High Risk

The first list of symptoms used to identify patients at risk is that of the negative symptoms of schizophrenia (Zdanowicz et al. 2013, Zdanowicz et al. 2014). It includes 14 symptoms:

1) Affective flattening;
2) Alogia;
3) Avolition (inability to initiate and persist in activities);
4) Inappropriate affects;
5) Anhedonia (lack of pleasure);
6) Dysphoria (discordant mood compared to the situation);
7) Sleep disorders;
8) Loss of appetite;
9) Psychomotor disorders;
10) Attention deficit disorders;
11) Confusion and disorientation;
12) Memory disorders;
13) Lowawarenessof the disorder;
14) Depersonalisation / derealisation.

It was quickly realized that, apart from the first three symptoms, none of these were specific nor sensitive enough to identify at risk subjects, especially among adolescents.

This listwas then restructured and reduced to seven negative symptoms (1 to 7) to which two positive symptoms were added (8 and 9):

1) Social isolation, or net withdrawal;
2) Net handicapped functioning;
3) Clearly weird behaviour;
4) Lack of hygiene and care given to the person;
5) Flat or inappropriate affects;
6) Avolition;
7) Digressive speech;
8) Odd beliefs or magical thinking;
9) Unusual perceptual experience;

Unfortunately, validation studiesof this list have not been successful either because some of these symptoms may be due to the side effects of neuroleptics or to a depressive component. Researchers have then turned their attention to the predictive value of the positive - however attenuated - symptoms (Meeset al. 2011). Two scales comprising attenuated positivesymptoms mixed with negative symptoms were used: the SOPS (Scale of Prodromal Symptoms) and the PACE (Personal Assessment and Crisis Evaluation). The SOPS, for example, is a scale that has four axes of symptoms: five positive items, six negative items, four disorganized items and four items measuring general symptoms. It attempts to quantitatively measure symptoms on a scale of 0-6. A score between 3 and 5 on any axis leads to UHR identification and a top score of 6 indicates a probable psychotic state. Overall, we consider that these scales predict a risk of 30-35% for UHR in developing a psychotic disorder in the 1-2 years following their identification. These scales have therefore limited specificity. To increase it, other prediction algorithms were added such as symptoms that are considered more" basic", such as those derived from "Basic Symptoms Criteria" or from radiographic images by magnetic resonance imaging (MRI). Although these trials have increased diagnostic and predictive sensitivity, they also led to some confusion. This confusion is exacerbated by the competition between the scales in terms of which has the earliest predictive power. Some therefore believe that the symptoms of the Basic Symptoms Criteria (BSC) are earlier than those included in the Attenuated Psychotic Symptoms Scale (APS) or in the Brief Limited Intermittent Psychosis Symptoms (BLIPS). The latter scale was developed as part of an attempt to classify mental states at risk of psychosis (ARMS At Risk Mental State). Finally during the last five years, these results have also been questioned by the discovery that UHR subjects displayed much more frequently an impressive array of various mental disorders such as depressive, anxiety, and other disorders rather than psychosis.

DISCUSSION

It is interesting to note from the history of all these attempts that researchers were initially interested in identifying schizophrenia with negative and insidious symptoms, and that as research went on, positive symptoms became increasingly present in the diagnostic criteria for UHR. Pharmacological studies on the effectiveness of prevention are restricted to the UHR. We can therefore raise the question of the therapeutic attitude (Zdanowicz 2007) to adopt with a young man who would display only "pre negative-symptoms"? For UHRs, the question of prescription is not much easier. If we know that 60% of them will display a full range psychotic disorder, does this justify the prescription of neuroleptics to 100% of them? Accessibility to health care is one of the determining elements of answer to this question. If no close monitoring is possible, then prescribing neuroleptics would mean giving the medication to someone who does not need them in two out of five cases, and, conversely, not prescribing poses a serious risk in three out of five cases... If close monitoring is possible, we think that the prescription of neuroleptics should be avoided because older data show that even in the presence of clear symptoms among adolescents, five years at least are necessary to confirm the diagnos of schizophrenia.

CONCLUSION

1) YES these psychotic and particularly schizophrenic disorders are serious and require the prescription of neuroleptics BUT 2) At least 40% do NOT display a chronic evolution and the "deposit" forms should be reserved for certain situations; 3) YES, schizophrenia has a peak prevalence at 18, and young people must be monitored, However 4) Our ability to achieve pre-diagnosis is limited. If prescribing neuroleptic drugs to all at-risk youth might prevent the onset of the disorders, it would also result in prescribing them to someone who does not need them two out of five times. In total, from these four arguments, only one is valid, and the remaining three are only partially valid; nevertheless, since the advent of second generation neuroleptic drugs, their consumption has increased by 14% in 10 years.

Acknowledgements: None.

Conflict of interest: None to declare.

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