Factors that influence patients' attitudes to antipsychotic medication

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Abstract

Objective: **The aim of this study was to investigate the attitudes to medication in relation to insight, purpose in life, symptoms and sociodemographic factors among a cohort of stable patients with a diagnosis of schizophrenia and schizoaffective disorder.**

Method: **We included 70 patients with a diagnosis of schizophrenia and schizoaffective disorder attending a Dublin suburban mental health service. All participants were 18 years or older and were excluded if they had a learning disability, acquired brain injury resulting in unconsciousness, and psychosis secondary to a general medical condition or illicit substance misuse. All participants were given self report questionnaires which included Drug Attitude Inventory (DAI-30), Birchwood Insight Scale, and Purpose in Life test. Symptoms were assessed using the Scale for Assessment of Positive and Negative symptoms. All data was analysed using the Statistical Package for the Social Sciences.**

Results: **We found that 86% (n = 60) of the participants had positive attitudes to medication, and 82% (n = 58) had good insight into their illness. Only 27% (n = 19) were found to have a definite purpose in life. There was a significant negative relationship between attitudes to medication and delusions ($r = -0.25$, $n = 70$, $p < 0.05$) and a significant positive relationship between insight and attitudes to medication ($r = 0.0.28$, $n = 70$, $p < 0.05$).**

Conclusion: **Many factors are involved in the multifaceted issue of attitudes to medication. Researchers must realise that these factors do not remain constant and may change with time and over the course of illness and treatment.**

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Introduction

It is estimated that about one in four people do not fully adhere to prescribed medication.[1] Considering the enormous personal, human, familial and economic cost it is surprising that more research is not conducted in this area. For people with schizophrenia, non adherence to treatment is a major reason for relapse[2] and has been described as the single most important cause of re-admission to hospital.[3] It is also associated with increased involuntary admissions, longer hospital stay, slower rate of recovery from psychosis[4] and an increased risk of suicide.[5]

Poor adherence is therefore considered a critical barrier to treatment success in schizophrenia and related mental disorders and remains one of the leading challenges to healthcare professionals. It is however important to acknowledge that non adherence is a common behaviour which is not confined to mental illness. Approximately 50% of people with any long-term illness have poor adherence and reduced compliance with their medication, which is similar to the proportion of patients with schizophrenia.[6] Patient characteristics that may lead to poor adherence for any illness include advanced age, cognitive impairment, depression, the disease being treated, the potential for adverse effects and attitudes and beliefs about medication.

Attitudes toward treatment are important in schizophrenia and related disorders due to their influence on adherence and compliance. Several studies have reported the importance of positive attitudes to treatment in improving adherence,[7,8] whereas negative attitudes to treatment among people with mental illness are known to have a negative impact on adherence[9,10] and future compliance.[11]

A person's attitudes to treatment can be influenced by a variety of factors including; the patient's views on the positive and negative aspects of taking medication, the belief that medication is only taken when one is ill and not when well (model of health vs. illness), the nature of patient's relationship with the physician, their perceived locus of control, and the belief that taking medication will prevent relapse and will not be harmful to them.[12]

Having insight,[13,14] lack of co-morbid substance misuse,[15] less psychopathology,[8] and better family and social relationships are associated with more positive attitudes to medication, adherence and compliance. Additionally, the purpose in life test measures the sense of purpose and meaning in an individual's life,[16] and is significant to psychological and mental wellbeing,[17] recovery, adjustment to illness[18] and quality of life of patients. Lower scores on purpose in life have

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been associated with first episode psychosis and a longer duration of untreated illness,[19] however little is known about purpose in life among patients with chronic psychotic illness and its influence on medication adherence and attitudes to treatment in such patients. Although previous studies have shown that attitudes to medication are associated with the above mentioned clinical and sociodemographic factors, few have examined the association of these variables within the same sample.

We examined the attitudes to medication among a cohort of stable Irish patients with a diagnosis of schizophrenia and schizoaffective disorder. Furthermore, we sought to examine the relationship between attitudes to medication and sociodemographic as well as clinical variables.

Method

The setting for the study was a community based psychiatric service in South East Dublin serving 172,000 people approximately. After receiving approval from the ethics committee, we recruited patients for the Resource for Psychosis Genomics in Ireland (RPGI) study from patients with a history of psychotic illness. The RPGI is a multi-centre case control study with the objectives of establishing a scientifically valuable, high integrity bank of DNA and tissue samples with associated genotypic and phenotypic data characteristics.

The aims of RPGI are identification of new susceptibility genes, exploration of the relationship between phenotype and genotype, and exploration of the interactions between different genes, and genes and the environment in order to facilitate research into the aetiology and management of psychoses.

For the RPGI study, we randomly selected patients from the consultant's case list if they had history of at least one psychotic episode and asked them to participate by letter, telephone call and face to face to explain the nature and purpose of the study. We invited 350 people to participate in the RPGI study. Of these, 110 were either eligible or consented to participate.

For the purpose of our smaller study we only included 70 patients with a diagnosis of schizophrenia or schizoaffective disorder. There were no significant clinical or sociodemographic differences in the participants who were excluded from the study. The inclusion criteria were age over 18 years, no history of learning disability or acquired brain injury resulting in unconsciousness, and psychosis not secondary to a general medical condition or illicit substance misuse. Diagnosis of schizophrenia and schizoaffective disorder was confirmed clinically by using Structured Clinical Interview for DSM-IV *(SCID, APA; 1994)* and review of case notes. We evaluated symptoms using Scale for the Assessment of Positive Symptoms *(SAPS, Andreasen, 1984)* and Scale for the Assessment of Negative Symptoms *(SANS, Andreasen, 1983)* and used Global Assessment of Function (GAF) scale *(Axis V, DSM IV-TR, APA: 1994)* to rate the social, occupational and psychological functioning of the participants. All the participants gave written informed consent for inclusion in the study.

The participants were given standardised self report questionnaires after their initial assessments and were asked to return these questionnaires in self addressed envelopes provided. We measured attitudes to medication using the Drug Attitude Inventory (DAI-30) which is a 30-item self-report measure developed by Hogan and Awad.[12] The DAI-30 has seven constituent subscales; subjective positive aspects of taking medication, subjective negative aspects of taking medication, health vs. illness, physician's advice, locus of control, relapse prevention, and harm.

Each subscale measures a particular aspect of patient's attitude towards treatment, eg. the positive aspects subscale measures whether a patient can recognise many of the positive aspects of taking medication, the physician's advice subscale measures whether a patient has a positive or a negative view of taking his physician's advice, the locus of control subscale assesses whether a patient believes others have more influence over their treatment, and the subscale of relapse prevention measures whether a patient believes that medication has the ability to prevent relapse.

Assessment of each subscale is based on patients' response to particular statements, eg. 'medication is taken only because of pressure from others', or 'medication is taken of own free choice' helps assess the subscale of locus of control, and 'it is up to the doctor to decide when medication should be stopped' and 'I know better than the doctor when to stop medication' assesses patients' attitude towards the physician's advice.

Each item on the DAI scale is rated by the patient as either true or false to produce a total score ranging from -30 to +30 with a positive score suggesting positive attitudes to medication and a negative score suggesting negative attitudes to medication.

We evaluated insight using the Birchwood Insight Scale which is an eight-item self-report scale.[20] It measures the degree of insight in patients, with higher scores indicating greater levels of insight. We used a cut off score of nine or more on the insight scale to indicate presence of insight.[20]

The Birchwood Insight Scale has three constituent subscales; recognition of illness, recognition of need for treatment and ability to relabel symptoms as pathological. A cut off score of three or more was used to indicate presence of insight for each of the subscales. We measured purpose in life using the Purpose in Life Test[16] which is a 20-item self-report questionnaire with a maximum score of 140. A score higher than 112 indicates a presence of purpose in life and a score less than 92 is considered to indicate absence of a definite purpose in life.[21]

Statistical analysis

We analysed the data using the Statistical Package for Social Sciences (SPSS). We investigated the relationship between attitudes to medication and different sociodemographic variables using Pearson product-moment correlation co-efficient. Logistic regression analysis was performed to assess which variables associated with attitudes to medication.

Results

The participants in our study were predominantly male, single, unemployed outpatients with an average duration of illness of 20 years *(see Table 1)*. Most of the participants (86%, n = 60) had positive attitudes to treatment and good insight into their illness (83%, n = 58) but only 27.1% (n = 19) had presence of a definite purpose in life.

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When DAI-30 was divided into its subscales, most of the participants 86% (n = 60) had a positive response on the health vs. illness subscale, 81% (n = 57) had a positive response on the subjective positive aspects of taking medication subscale, 80% (n = 56) had a positive response on the relapse prevention subscale, 77% (n = 54) had a positive response on the physician's advice subscale, and 77% (n = 54) had a positive response on the locus of control subscale.

On the subscale of subjective negative aspects 66% (n = 46) of the participants gave a positive response, suggesting that they did not have a tendency to dwell on the negative aspects of taking medication. However, on the DAI subscale of harm, only 53% (n = 37) of the participants had a positive response suggesting that they believed taking medication could cause them harm. The inter relationships between attitudes to medication, insight, clinical and sociodemographic variables are shown in *Table 2*.

Attitudes to medication and demographic variables

The mean score for DAI-30 was 16.56 (SD = 11.7). We did not find any significant relationship between the overall DAI score and any of the sociodemographic variables. The only significant relationship observed between the DAI subscales and sociodemographic variables was a negative relationship between the subscale of physician's advice and employment status ($r = -0.26$, $p < 0.05$).

Attitudes to medication and symptoms

There was a significant negative relationship between higher SAPS delusion score and overall attitudes to medication ($r = -0.25$, $p < 0.05$). The only significant association between symptoms and subscales of the DAI was a negative association between subjective recognition for positive aspects of treatment and higher scores on delusions ($r = -0.28$, $p < 0.05$). No other relationship between symptoms and any other subscales of the DAI was observed.

Attitudes to medication and Insight

Higher total insight score was significantly related to overall positive attitudes to treatment ($r = 0.28$, $p < 0.05$). However; the total insight score was not related to any of the subscales of DAI. There was a strong significant relationship between the insight dimension of recognition of need for treatment and the overall attitudes to medication ($r = 0.64$, $p < 0.01$).

The insight subscale recognition of need for treatment was also significantly related to the DAI subscales of subjective positive aspects of medication ($r = 0.53$, $p < 0.01$), locus of control ($r = 0.62$, $p < 0.01$), patients' model of health vs. illness ($r = 0.45$, $p < 0.01$), and patients' perception of medication causing harm ($r = 0.49$, $p < 0.01$). However, no association was seen between the insight subscale of recognition of need for treatment and the DAI subscales subjective negative aspects, relapse prevention or physician's advice. Similarly, there was no significant relationship between the insight subscales of recognition of illness or re-label symptoms with either the overall attitudes to treatment or any of the DAI subscales.

Attitudes to medication and other clinical variables

There was a significant association between taking two or more neuroleptics and the subscales of harm ($r = 0.24$, $p < 0.05$), locus of control ($r = 0.27$, $p < 0.05$), and physician's advice ($r = 0.27$, $p < 0.05$). However, no relationship was observed between attitudes to medication and duration of illness, treatment setting, past admission status, number of hospitalisations, being prescribed depot medication, and illicit substance misuse.

Table 1: Clinical and sociodemographic characteristics of the sample

Gender	Male	48 (68.6%)
	Female	22 (31.4%)
Age	Mean	42.63
	SD	12.03
Duration of illness	Mean	19.80 yrs
	SD	10.20
	More than 10 years	75.7%
Marital Status	Single	53 (75.7%)
	Married/Divorced/Separated	17 (24.3%)
Education	Graduated secondary school	47 (67.1%)
	Did not graduate secondary school	23 (32.9%)
Employment status	Employed	29 (41.4%)
	Unemployed	41 (58.6%)
Treatment setting	Inpatients	13 (18.6%)
	Outpatients	57 (81.4%)
No of Hospitalisations	3 or less	31 (44.3%)
	> 3	39 (55.7%)
Time since last admission	1-4 weeks	05 (7.1%)
	> 4 weeks	65 (92.9%)
Past admission status	Voluntary	32 (45.7%)
	Involuntary ever	38 (54.3%)
GAF (Global Assessment of Function)	> 60	27 (38.6%)
	60 or less	43 (61.4%)
Medication at interview	1 Neuroleptic	27 (38.6%)
	2 or more Neuroleptics	43 (61.4%)
Prescribed Depot Neuroleptic	Yes	12 (17.1%)
	No	58 (83.9%)
Drug use	Lifetime	32 (45.7%)
	Past month	10 (14.3%)
Alcohol Abuse	Lifetime	29 (41.4%)
	Past month	09 (12.9%)

Attitudes to medication and level of functioning

There was a significant and positive relationship between higher scores on global level of functioning and overall attitudes to medication ($r = 0.30$, $p < 0.05$). Better level of functioning was also significantly related to the DAI subscale of positive aspects of taking medication ($r = 0.31$, $p < 0.01$).

Attitudes to medication and purpose in life

We failed to find any significant relationships between attitudes to medication and purpose in life ($r = 0.47$, not statistically significant).

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Table 2: Correlations between DAI-30, its subscales and clinical and sociodemographic variables

Measuring Scale/Subscales	Variable	Correlations r	Significance (P value)
DAI-30	GAF	r = +0.30	< 0.05
	Delusions	r = -0.25	< 0.05
	Insight	r = +0.28	< 0.05
	Recognition of need for treatment	r = +0.64	< 0.01
Subjective positive aspects	Delusions	r = -0.28	< 0.05
	GAF	r = +0.31	< 0.01
	Recognition of need for treatment	r = +0.53	< 0.01
Subjective negative aspects			
Physicians' advice	Two or more neuroleptics	r = +0.27	< 0.05
	Employment status	r = -0.26	< 0.05
	Recognition of need for treatment	r = +0.26	< 0.05
Locus of control	Two or more neuroleptics	r = +0.27	< 0.05
	Recognition of need for treatment	r = +0.62	< 0.01
Health vs. illness	Recognition of need for treatment	r = +0.45	< 0.01
Relapse prevention	Recognition of need for treatment	r = +0.29	< 0.05
Harm	Two or more neuroleptics	r = +0.24	< 0.05
	Recognition of need for treatment	r = +0.49	< 0.01
Insight	GAF	r = +0.31	< 0.01
	Age	r = -0.24	< 0.05
	Duration of Illness	r = -0.35	< 0.01
Re-labelling of symptoms	GAF	r = -0.23	< 0.05
	Age	r = -0.26	< 0.05
	Duration of Illness	r = -0.33	< 0.01

DAI-30 = Drug Attitude Inventory, GAF = Global Assessment of Function.

Insight, clinical and sociodemographic variables

The mean score for Birchwood insight scale was 10.17 (SD = 1.96). We found that patients with higher total insight scores had significantly better level of functioning ($r = 0.31$, $p < 0.01$) than patients with poor insight into their illness, and poor insight into illness was also associated with a longer duration of illness ($r = -0.35$, $p < 0.01$) and older age ($r = -0.24$, $p < 0.05$).

Another important observation in our study was that a, longer duration of illness ($r = -0.33$, $p < 0.01$), older age ($r = -0.26$, $p < 0.05$) and poor level of functioning ($r = -0.23$, $p < 0.05$) were associated with a reduced likelihood of patients to re-label symptoms as pathological. However, these three variables had no significant relationship with the insight dimensions of recognition of illness or recognition of need for treatment.

Purpose in life

The mean score for the Purpose in Life Test was 97 (SD = 19.9) with 27.1% (n = 19) of the participants having a purpose in life and 37.1% (n = 26) lacking a definite purpose in life. We did not find any significant associations between purpose in life and other clinical and sociodemographic variables.

Logistic regression

We used binary logistic regression models to predict the relationship between attitudes to medication and the clinical and sociodemographic variables. Using DAI total and its seven constituent subscales as the dependant variables, we ran eight separate models to see which clinical and sociodemographic factors were significant in predicting a relationship with patient attitudes to treatment. The independent variables we used for each of the models were age, gender, marital status, educational achievement, duration of illness, employment status, treatment setting, number of hospitalisations, time since last admission, past treatment status, level of functioning, alcohol and drug abuse, medication at interview, and whether receiving depot medication.

We observed that of the eight models we ran, only one overall model was significant when the subjective positive subscale of the DAI-30 was used as the dependant variable ($\chi^2 = 43$, $df = 20$, $p = 0.02$). Of all the independent variables used within that model, only recognition of illness (Wald statistic = 4.06, $df = 1$, $p < 0.05$) and employment status (Wald statistic = 3.99, $df = 1$, $p < 0.05$) were significant.

However, when tested on an individual basis the significance of these variables was lost which lead to our discarding of the results. We failed to find any significant relationship between any of the other subscales and the clinical and sociodemographic characteristics.

Discussion

The participants in our study had a predominantly positive

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response with more than 85 % reporting positive attitudes to medication. This might be viewed as at variance with previous research which suggests that approximately half to two thirds of patients with schizophrenia and schizoaffective disorder have poor attitudes to medication.[8,22] However, in the present study only a modest proportion (19%) of the sample were inpatients at the time of the assessment and the majority were a stable and chronic cohort of patients with a long duration of illness.

The main aim of our study was to identify the clinical and sociodemographic variables which can predict future adherence. We found that good insight, better global functioning, having fewer positive symptoms, being unemployed, and receiving two or more neuroleptics at the time of interview were associated with positive attitudes to medication.

We also found that having delusions led to poor attitudes to medication and patients with higher scores on delusions also failed to recognise the positive aspects of taking medication. This finding is consistent with reports of previous studies reporting more positive attitudes to medication in patients with less psychopathology and fewer symptoms.[8,13]

Patients in our study had more positive attitudes to medication if they had better insight into their illness. This association was even stronger for those patients who recognised the need for having treatment. This finding is consistent with previous studies investigating attitudes to treatment, insight and compliance which have indicated that patients with better insight are more likely to accept treatment than patients with poor insight[23,24] and especially if they recognise the importance of taking their treatment.[25] The strong associations observed between the insight dimension of recognition of need for treatment and attitudes to medication has important consequences as measures to improve this dimension of insight can lead to increased adherence and improved attitudes to treatment.

We found that patients on two or more neuroleptics at the time of interview were more likely to adhere to their physician's advice and believe that taking medication will not cause them harm.

They were also more likely to believe that they had more control over their medication intake than others. This finding is in contrast to studies reporting that polypharmacy is associated with negative health outcomes and leads to negative health beliefs and reduced adherence among patients.[26,27] However further research is needed to assess the relationship of polypharmacy, health beliefs and attitudes to treatment among patients with chronic mental illness.

As expected, patients in our study with good insight into their illness had better level of functioning. An important and significant observation was the negative relationship between older age and longer duration of illness with total insight scores and only the insight dimension of re-labelling of symptoms. Recognition of need for treatment which was the insight dimension most associated with positive attitudes to treatment and its subscales had no relationship either with age or duration of illness

Although like Cabeza *et al*[8] we observed significant relationships between attitudes to medication, insight, symptoms and better overall functioning, we failed to find any relationship between the number of hospitalisations and attitudes to medication. The mean score for DAI-30 was higher in our study with 86% of the participants reporting positive attitudes to medication compared with 75% in the Cabeza *et al* study. However, there were important sociodemographic and methodological differences in the two studies as all the participants in the Cabeza *et al* study were inpatients and were interviewed prior to their discharge, whereas only a small proportion of our participants (19%) were inpatients at the time of the assessment. Participants in our study were also much older and three-quarters had duration of illness of more than 10 years compared to only one-third in the Cabeza *et al* study.

Similarly, Kamali *et al* reported insight into illness, current co-morbid substance misuse and receiving depot medication as important variables which influence attitudes to their treatment and result in poor compliance.[15,28] Furthermore, they also found that participants who were irregularly compliant had more negative subjective or dysphoric attitudes to medication than those who were regularly compliant. However, all 87 participants in their study were inpatients, were admitted over a 12 month period and had a mean duration of illness of 13 years compared to our subjects the majority of whom were attending outpatients department and had a much longer duration of illness.

It must be stressed here that differences in findings between the current study and previous studies may reflect the fact that attitudes to treatment and the factors that influence it may change according to the phase and course of illness.

We failed to observe any significant relationship between attitudes to medication and age, gender, educational achievement, history of substance misuse or between purpose in life and attitudes to medication, and purpose in life and insight.

Despite being reported as strong predictors of adherence, we did not find any significant relationship between either marital status[29] or receiving depot medication and attitudes to treatment in our study. The small number of participants within the two subgroups is a plausible explanation and a limitation of the study which may have resulted in the failure of any significant associations between these variables and attitudes to treatment.

Similarly, on logistic regression analysis, none of the clinical or sociodemographic variables included in our study predicted attitudes to medication, and employment status and the insight dimension of recognition of illness were significant only within the 'subjective positive subscale' model. The large number of statistical tests involved in the study for analysis of various clinical, social and demographic variables is also a limitation of the study. We could have considered a Bonferroni correction to avoid a type I error by setting a more conservative critical value. However, this was not done as we considered that there would be an even greater risk of making a type II error because of the modest sample size in our study.

Another limitation of our study is that results are relevant to largely stable outpatient samples only and are not representative of the entire spectrum of people with schizophrenia and schizoaffective disorder. It could also be argued that over reliance on self-report questionnaires can lead to more positive responses as patients may wish to please researchers.

Despite the high levels of positive attitudes to treatment reflected in the total DAI score and the majority of its

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subscales in this sample, it is important to note that almost half of the patients had a belief that medication did them harm. Further studies of interventions to better inform patients about antipsychotic medication may help alleviate such concerns.

Conclusion

Many factors are involved in the multifaceted issue of attitudes to treatment. These factors do not remain constant and may change with time and over the course of illness and treatment. Despite its importance, adherence to treatment is an individual patient behaviour and is difficult to objectively measure, monitor and improve. Clearly, stable outpatients' attitudes to medication are generally positive and are associated with insight into their illness. The three dimensions of insight can also vary independently and efforts to improve attitudes to treatment may be enhanced by focusing on the dimension of recognition of need for treatment.

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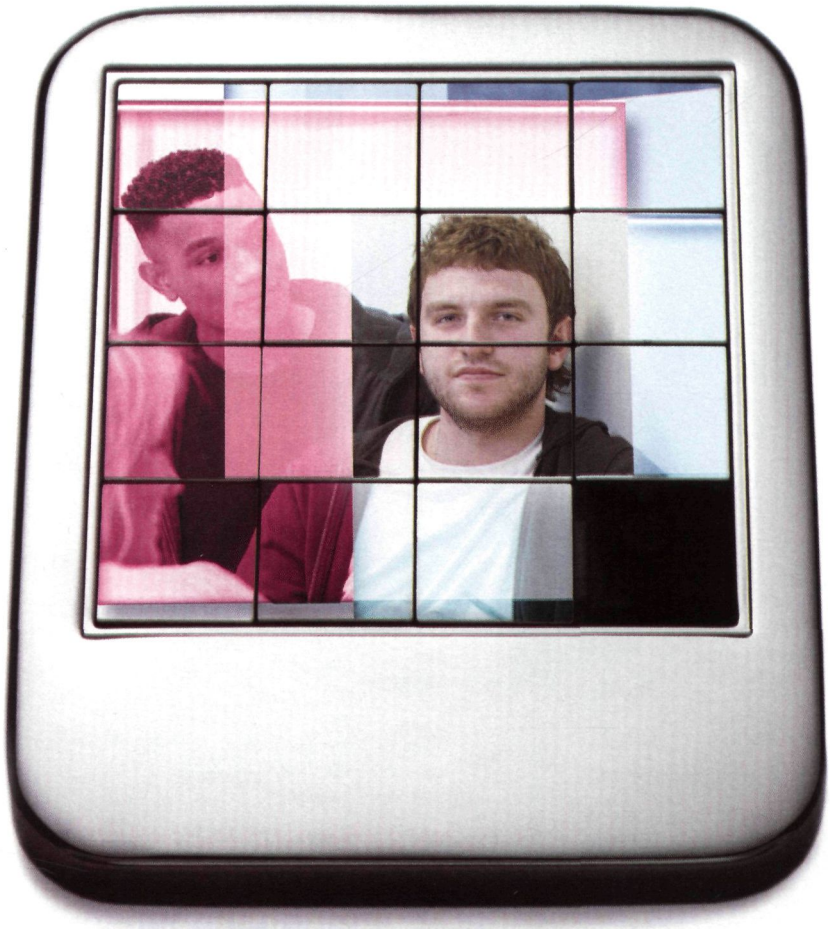

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For the person within

INVEGA®
PALIPERIDONE
Prolonged-Release Tablets

Invega® is efficacious across all PANSS scores with symptom reduction as early as day 4.[1]

Overall incidence of common side-effects, in clinical trials, similar to placebo at the recommended dose of 6mg.[2–4]

JANSSEN-CILAG Ltd

INVEGA® PRESCRIBING INFORMATION INVEGA® PROLONGED RELEASE TABLETS (3 mg, 6 mg and 9 mg) **ACTIVE INGREDIENT:** 3 mg, 6 mg or 9 mg paliperidone. *Please refer to Summary of Product Characteristics (SmPC) before prescribing.* **INDICATION:** INVEGA (paliperidone) is indicated for the treatment of schizophrenia. **DOSAGE & ADMINISTRATION:** ***Adults:*** recommended dose is 6 mg once daily in the morning with or without food (do **not** alternate). Initial dose titration not required. Dose may be adjusted within recommended range (3 mg to 12 mg once daily) after clinical reassessment. Adjust dose in increments of 3 mg/day at intervals of > 5 days. Swallow tablets **whole** with liquid. ***Children and adolescents:*** Not recommended. ***Elderly:*** Caution in elderly dementia patients with stroke risk factors. ***Renal impairment:*** 3 mg initial dose recommended in patients with mild to moderate renal impairment. Can increase to 6 mg once daily based on clinical response and tolerability. 3 mg every other day recommended initial dose in severe renal impairment. Do not use in patients with creatinine clearance below *10 ml/min.* ***Hepatic impairment:*** *No dose adjustment for mild or moderate hepatic impairment.* Caution in severe hepatic impairment. **CONTRAINDICATIONS:** Hypersensitivity to paliperidone, risperidone, or excipients. **SPECIAL WARNINGS & PRECAUTIONS:** ***Cardiovascular disease:*** Caution in patients with known cardiovascular disease, or family history of Q-T prolongation. INVEGA may induce orthostatic hypotension in some patients. Use with caution in cerebrovascular disease and conditions that predispose to hypotension. ***Neuroleptic Malignant Syndrome:*** Discontinue INVEGA if symptoms/signs develop. ***Tardive dyskinesia:*** If signs/symptoms appear, consider discontinuing all antipsychotics, including INVEGA. ***Patients with diabetes mellitus/ hyperglycaemia:*** Appropriate clinical monitoring is advisable (rare increases in blood glucose have been reported). ***Patients with seizures:*** Caution where there is a history of seizures/ other conditions that potentially lower the seizure threshold. ***Patients with dysphagia:*** Do not administer to patients with significant swallowing difficulty **or** known gastro-intestinal strictures. ***Patients with decreased gastro-intestinal transit time:*** Reduced absorption of paliperidone may result. ***Patients with renal impairment:*** See Dosage. Do not use in patients with creatinine clearance below 10 ml/min. ***Patients with hepatic impairment:*** See Dosage. Caution in severe hepatic impairment. ***Elderly patients with dementia:*** Use with caution in elderly dementia patients with risk factors for stroke. ***Priapism:*** no cases reported in clinical trials with INVEGA; paliperidone may be associated with this risk due to its alpha-adrenergic blocking effects. ***Body temperature regulation:*** Care when prescribing to patients experiencing conditions which may contribute to core body temperature elevation. ***Anti-emetic effect:*** Observed in paliperidone preclinical studies; if occurs in human patients may mask signs and symptoms of overdosage with certain medicines, or of medical conditions such as intestinal obstruction, Reye's syndrome, brain tumour etc. ***Lactose content (3 mg tablets only):*** Avoid in patients with rare hereditary galactose intolerance, Lapp lactase deficiency or glucosegalactose malabsorption. **SIDE EFFECTS:** The most frequently reported ADR's in INVEGA treated subjects in clinical trials were: Headache, tachycardia, akathisia, sinus tachycardia, extrapyramidal disorder, somnolence, dizziness, sedation, tremor, hypertonia, dystonia, orthostatic hypotension, dry mouth. ***Uncommon:*** Anaphylactic reaction, increased appetite, nightmare, dizziness (postural), dyskinesia, Grand [illegible]thmia, hypotension, ischaemia, muscle rigidity, amenorrhoea, breast discharge, erectile dysfunction, galactorrhoea, gynaecomastia, irregular menstruation, oedema. ***Extrapyramidal Symptoms (EPS):*** No difference observed between placebo and the 3 mg and 6 mg doses of INVEGA. Dose-relatedness for EPS was seen with higher INVEGA doses (9 mg and 12 mg). ***Laboratory Test Serum Prolactin:*** median increases observed in 67% of subjects in clinical trials with INVEGA however adverse events that may suggest increase in prolactin levels were reported in 2% subjects overall. ***Weight gain:*** clinical trials revealed similar incidence of weight gain for INVEGA 3 mg and 6 mg compared with placebo; higher incidence of weight gain for INVEGA 9 mg and 12 mg. ***Class effects:*** QT prolongation, ventricular arrhythmias, sudden unexplained death, cardiac arrest and Torsade de pointes may occur with antipsychotics. **Refer to SmPC for other side effects. PREGNANCY:** INVEGA should not be used during pregnancy. **LACTATION:** INVEGA should not be used while breastfeeding. **INTERACTIONS:** Caution prescribing INVEGA with medicines that prolong QT interval e.g. class IA and class III antiarrhythmics, some antihistaminics, some *other antipsychotics, some antimalarials.* ***Potential for INVEGA to affect other medicines:*** Not expected to cause clinically important pharmacokinetic interactions with medicines metabolized by cytochrome P-450 isozymes. Use with caution in conjunction with: centrally acting medicines e.g. anxiolytics, antipsychotics, hypnotics, opiates, or alcohol; medicines known to lower seizure threshold i.e. phenothiazines, butyrophenones, tricyclics, SSRI's, tramadol, mefloquine etc; medicines capable of inducing orthostatic hypotension (an additive effect may be observed when INVEGA is co-administered); levodopa and other dopamine agonists (paliperidone may antagonize their effect - use the lowest effective dose of each treatment if this combination must be prescribed e.g. end-stage Parkinson's disease). ***Potential for other medicines to affect INVEGA:*** Co-administration of INVEGA once daily with carbamazepine 200 mg twice daily decreases plasma concentration of paliperdone by 37% (induction of renal P-gp by carbamazepine increases renal clearance). *In vitro* studies have shown that paliperidone is a P-glycoprotein (P-gp) substrate. Re-evaluate/increase INVEGA dose at carbemazepine initiation. Other P-gp inducers e.g., rifampicin, St. John's wort may have similar effects. No indications from *in vitro* and *in vivo* studies that isozymes CYP2D6 and CYP3A4 are significant in the metabolism of paliperidone. Concomitant administration of INVEGA and paroxetine (a potent CYP2D6 inhibitor) showed no clinically significant effect on paliperidone pharmacokinetics. Metoclopramide and other medicines affecting G.I. transit time may alter paliperidone absorption. Do not use INVEGA with oral risperidone as additive paliperidone exposure may occur. **LEGAL CATEGORY:** POM **PRESENTATIONS, PACK SIZES & PRODUCT LICENCE NUMBERS:** 3 mg, 6 mg, 9 mg prolonged release tablets. EU/1/07/395/001,1/07/395/006 and 1/07/395/011. Blister packs of 28 tablets. **MARKETING AUTHORISATION HOLDER:** JANSSEN-CILAG INTERNATIONAL NV, Turnhoutseweg 30, B-2340 Beerse, Belgium. **FURTHER INFORMATION IS AVAILABLE FROM:** Janssen-Cilag Ltd, 50–100 Holmers Farm Way, High Wycombe, Buckinghamshire HP12 4EG UK. Prescribing Information last revised: 01/2009. PIVER20.01.09.

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