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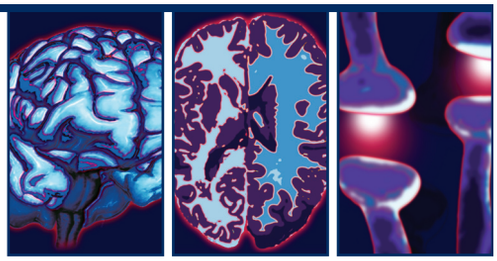

Duration of illness and duration of untreated illness in relation to drug response in psychiatric disorders

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Practice points

- Duration of illness (DI) and duration of untreated illness (DUI) are predictors of poor outcome in the different psychiatric disorders.
- A prolonged DI and DUI are associated with brain abnormalities particularly in schizophrenia.
- Brain abnormalities can play an important role in determining poor treatment response in patients with long DI and DUI.
- DI/DUI has to be taken into account for explaining differences in the efficacy of second-generation antipsychotics in schizophrenics.
- A long DI/DUI is probably associated with less sensitivity to pharmacological treatments and, in particular, to second-generation antipsychotics.

SUMMARY Recent literature considers duration of illness (DI) and duration of untreated illness (DUI) as important factors influencing outcome in many psychiatric conditions. The aim of the present article is to analyze the relationship between DI and DUI, and pharmacological response in the different psychiatric disorders with particular emphasis on neurodegenerative aspects. An updated review of the current literature was conducted through PubMed in order to compare different studies focused on DI and DUI, and treatment response in major psychoses and in depressive/anxiety disorders. A significant body of evidence shows that a prolonged DI and DUI is associated with brain abnormalities and poor treatment response, particularly in schizophrenia. Nevertheless, an increasing number of studies point toward a similar conclusion in mood and anxiety disorders as well, even though fewer studies have been published in this field. Given the relationship between a longer DI and DUI, and poor treatment response – not only in schizophrenia but also in mood and anxiety disorders – specific intervention programs aimed to reduce the latency to treatment are definitely envisaged.

Several studies indicate duration of illness (DI) and duration of untreated illness (DUI) as important variables predicting outcome in psychiatric disorders and, in particular, in psychotic ones [1].

Duration of untreated illness, defined as the interval between the onset of a psychiatric disorder according to the current classifications and the administration of the first pharmacological

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treatment, has been increasingly investigated as a predictor of clinical outcome and course across different conditions. In the case of schizophrenia the term DUI is frequently substituted with duration of untreated psychosis (DUP), which refers to the time between the onset of psychotic symptoms and the start of a pharmacological treatment. Negative symptoms, such as withdrawal or apathy, can be present in the prodomal phases of the illness [2]; however, psychotic symptoms (e.g., delusions, hallucinations and disorganization) are necessary to make a diagnosis of schizophrenia according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) criteria [3], and the terms DUI and DUP are interchangeable in most of the studies.

Duration of untreated illness represents a modifiable parameter [4–6], the reduction of which may positively influence the outcome and long-term course of specific mental conditions [7]. In fact, several studies indicate that a prolonged DUI is a negative prognostic factor in schizophrenia and increasing data point toward a similar conclusion in affective and anxiety disorders as well.

Several data indicate DI and DUI as variables predicting poor drug response in the different psychiatric conditions. On the other hand, a long DI and DUI have been associated with neurodegenerative aspects as demonstrated by a considerable number of studies. Some authors hypothesize that treatment resistance of chronic patients could be due to the neurodegenerative aspects associated with long DI and DUI [8]. The purpose of the present article is to review the literature regarding the relationship between DI and DUI and treatment response across the main psychiatric conditions. As neurodegenerative aspects are hypothesized to be the most important factors influencing pharmacological effectiveness, data indicating an association between DI and DUI, and brain changes are also described.

Methods

In order to provide an updated overview in relation to the influence of DI and DUI on brain changes and treatment response in the different psychiatric conditions, relevant articles were located by searching MEDLINE. Keywords used included 'Duration of Illness (DI)', 'Duration of Untreated Illness (DUI)' and 'Duration of Untreated Psychosis (DUP)', respectively matched with the terms 'treatment response', 'brain abnormalities', 'brain changes', 'Magnetic Resonance (MR)', 'Computed Tomography (CT)', 'Schizophrenia', 'Bipolar Disorder', 'Major Depressive Disorder', 'Anxiety Disorders' (Panic Disorder, Generalized Anxiety Disorder, Social Anxiety Disorder, Obsessive–Compulsive Disorder, Post-Traumatic Stress Disorder). Studies with the following definitions of DUI, DUP and DI were included:

- DUI: the time elapsing between the onset of a psychiatric disorder according to the DSM-IV-TR criteria and the administration of the first adequate pharmacological treatment according to the current guidelines;
- DUP: the time elapsing between the onset of psychotic symptoms in schizophrenic patients and the administration of the first antipsychotic treatment;
- DI: the time after the onset of a psychiatric disorder according to the DSM-IV-TR criteria.

Studies in which the terms DUI and DUP are not interchangeable were excluded.

Relationship between DI/DUI & brain structure in psychiatric disorders

Brain areas negatively associated with DI/DUI across the different psychiatric conditions are summarized in **Tables 1 & 2**.

Schizophrenia

Brain changes are associated with a long DI as demonstrated by numerous MRI studies. These brain changes appear particularly severe in the first years of illness, being similar to normal aging in late life [9]. Premkumar and colleagues suggest that the right middle frontal cortex is particularly vulnerable to the long-term effect of schizophrenic illness, whereas the dorsomedial prefrontal cortex, fusiform gyrus and cerebellum are affected by both a long DI and aging [10]. Another MRI study by the same group showed that there was a significant exponential relation between the DI and the volumes of prefrontal cortex, parieto-occipital cortex gray matter, thalamus and putamen, suggesting that these regions are susceptible to change if the disorder persists [11]. DI has been negatively associated with gray matter volume in prefrontal regions bilaterally, in the temporal pole on the left and the caudal superior temporal gyrus on the right [12]. In a 5-year MRI longitudinal study with 96 schizophrenic patients the progression

in left frontal density loss appeared to be related to an increased number of psychotic episodes, with atypical antipsychotics attenuating these changes [13]. The loss of prefrontal gray matter volume is confirmed by other previous studies [14]. Bilateral insular cortex volumes have been negatively correlated with DI [15]. No differences were found in thalamic volume between first-episode versus chronic schizophrenic patients [16].

An association between prolonged DUI/DUP and decreased temporal volume has been reported [17]. This observation was confirmed in a MRI trial in which a loss of the left planum temporal gray matter was associated with a long DUP, suggesting a role of this specific area in the initial phases of untreated psychosis [18]. Bangalore and colleagues investigated the effect of DUI on brain structures in minimally treated psychotic patients by MRI, finding that DUI inversely correlated with gray matter (i.e., the longer the DUI, the lower the gray matter density) of the left fusiform gyrus, left lingual gyrus, left declive and right parahippocampal gyrus [19]. Such results are consistent with the observations of a recent study reporting decreased gray matter in the left middle and inferior temporal, left occipital and left fusiform cortices [20]. Hippocampal volumes seem not to be altered by a long DUP [21], even though a very recent study reported that the length of DUP associated positively with reduced densities of the right limbic area and the right hippocampus [22]. Finally, a minority of dated studies failed to find a relationship between length of DUP and brain changes in schizophrenic patients [23,24].

Taken as a whole, the data mentioned earlier point to a negative effect of DI and DUI particularly in the first years of schizophrenia, with damage to different brain areas and a probable protective effects of atypical antipsychotics.

With regard to neurobiological mechanisms underlying schizophrenia, it has been hypothesized that the adverse effects on outcome associated with untreated psychosis may be biologically mediated. One toxicity model suggests that *N*-methyl-D-aspartic acid receptor hypofunctioning may induce psychosis and produce glutamatergically medicated excitotoxic damage in neurons at the same time [25]. Alternatively, prolonged stress, including stress resulting from untreated psychosis, may activate the hypothalamic–pituitary–adrenal axis, leading to greater glucocorticoid secretion, which, in turn, may contribute to neuronal damage [26].

Table 1. Brain areas involved in patients with long duration of illness.

Psychiatric disorders	Brain areas	Ref.
Schizophrenia	Right middle frontal cortex	[10]
	Dorsomedial prefrontal cortex	[10]
	Fusiform gyrus	[10]
	Cerebellum	[10]
	Parieto-occipital cortex	[11]
	Thalamus	[11]
	Putamen	[11]
	Temporal pole	[12]
	Caudal superior temporal gyrus	[12]
	Insular cortex	[15]
Bipolar disorder	Hippocampus	[27,28]
	Cerebellum	[27]
	Fusiform cortex	[27]
	Left middle frontal cortex	[29]
	Dorsolateral prefrontal cortex	[31]
Major depressive disorder	Hippocampus	[35]
	Subcallosal gyrus	[38]
Panic disorder	Left putamen	[40]
Obsessive–compulsive disorder	Hippocampus	[41]
	Amygdala	[41]

Bipolar disorder

Evidence of neurodegeneration in bipolar patients with a long DI is less robust compared with schizophrenic ones. A 4-year follow-up MRI study showed a greater gray matter loss in the hippocampus, cerebellum and fusiform cortex in 20 bipolar patients compared with healthy controls [27]. Other authors reported a loss of hippocampal volume in bipolar patients with a long DI [28]. DI in bipolar subjects has been inversely correlated with the cortical thickness of the left middle frontal cortex [29]. Lateral ventricles seem to be larger in multiple-episode bipolar patients compared with first-episode ones [30]. In particular manic episodes, but not major depressive episodes, would be associated with a gray matter reduction in dorsolateral prefrontal cortices [31]. On the other hand, other authors reported that the number of previous major mood episodes and DI were not significantly correlated with gray and white matter volume in bipolar disorder [32,33]. Finally, no correlations were found between DUI and white matter hyperintensities, a neuroimaging abnormality typical of bipolar disorder [34].

As mentioned earlier, brain neurodegenerative processes in bipolar patients seem to be less extensive than in schizophrenics and, being manic episodes, probably more 'toxic' than major depressive ones; studies comparing bipolar I and II are warranted to detect eventual differences in these two subgroups of patients.

Table 2. Brain areas involved in patients with long duration of untreated illness.

Psychiatric disorder	Brain area	Ref.
Schizophrenia	Left planum temporal	[18]
	Left fusiform gyrus	[19]
	Left lingual gyrus	[19]
	Left declive (cerebellum)	[19]
	Right parahippocampal gyrus	[19]
	Left middle temporal cortex	[20]
	Inferior temporal cortex	[20]
	Left occipital cortex	[20]
	Hippocampus	[22]
Bipolar disorder, major depressive disorder and anxiety disorders	No data	–

■ Major depressive disorder & anxiety disorders

The relation between neurodegenerative aspects and DI in patients with mood or anxiety disorders is still debated. The results of a recent meta-analysis suggest a relationship between hippocampal volume and DI in major depressed patients [35], probably as a consequence of a hypothalamic–pituitary–adrenal system dysfunction [36]. By contrast, hippocampal changes in patients with major depressive disorder and different DI were not shown in results of a previous study [37]. Patients affected by major depressive disorder and with more than three untreated depressive episodes were found to have smaller subcallosal gyrus volumes than healthy controls, while those with three or fewer past untreated episodes did not differ from controls [38]. A relationship between DI and global gray matter loss was reported for patients affected by major depressive disorder [39]. A loss of left putaminal gray matter volume was observed in patients with panic disorder and long DI [40]. DI in patients with obsessive–compulsive disorder (OCD) has been negatively correlated with hippocampus and amygdalar volumes [41]. By contrast, caudate nucleus volumes were not significantly correlated with DI in patients with OCD [42]. No relationship between hippocampus volumes and DI was found in patients affected by post-traumatic stress disorder [43].

Studies cited earlier show a positive association between DI and brain changes in major depressive disorder, panic disorder and OCD, however, these data are preliminary and need to be confirmed by future studies. No studies have investigated the effects of DUI on brain structure of patients affected by major depressive disorder or anxiety disorders.

DI/DUI & treatment response

■ Schizophrenia

Treatment response to antipsychotics has been negatively correlated with DI and DUI/DUP in schizophrenia. In a recent study, DI was found to be predictive of treatment response to olanzapine and risperidone during acute episodes of schizophrenia [44]. Similar results were found regarding eletroconvulsive therapy: long DI would portend poor response to eletroconvulsive therapy in 253 patients with treatment-resistant schizophrenia [45].

A longer DUP was associated with greater morbidity in the early course of schizophrenia: a systematic meta-analysis of 43 studies investigating the relationship between DUP and outcome in first-episode schizophrenia found that a prolonged DUP was associated with poor response to pharmacological treatment and no symptomatic/functional recovery [46]. A previous study by the same group found that a shorter DUP was associated with better clinical response, including improvement in overall psychopathology and negative symptoms. Furthermore, a longer DUP was found to predict more severe positive and negative symptoms and poorer social function at 1 year in 98 patients with first-episode schizophrenia [47]. The impact of the DUP prior to first psychiatric admission on the 15-year outcome in schizophrenia was analyzed by Bottlender and collaborators in 2003 [48]. They found that a longer DUP was associated with more pronounced negative, positive and general psychopathological symptoms as well as a lower global functioning 15 years after the first psychiatric admission. These data are confirmed by previous retrospective studies [49,50].

Of clinical interest, the relationship between DUP and outcome has been analyzed prospectively in different follow-up periods. An 8-year prospective naturalistic study by Harris [51] involving 318 first-episode psychotic patients found that a shorter DUP (≤3 months) correlated moderately with a better treatment response on positive symptoms and with a better social functioning and quality of life in comparison with a longer DUP (>3 months). Other studies confirmed the relation between a long DUP and a scarce pharmacological response on negative symptoms [5], as well on cognitive symptoms [47,52–55]. It has been reported that short DUP, associated with greater response to antipsychotic treatment, may underlie a subgroup with better prognosis; furthermore, a meta-analysis conducted by

Marshall and coworkers showed that patients with a long DUP were significantly less likely to achieve remission [56]. Haas and coworkers in 1998 examined the effect of DUP and DI on treatment response and the relation between these two variables [50]. Interestingly patients with a DUP of more than 1 year showed a worse response to pharmacological treatment during hospitalization compared with patients with a short DUP independently of the DI.

The length of DUP seems to be strongly associated with poor pharmacological response in schizophrenics. By contrast, a negative effect of DI on treatment response of schizophrenics is shown only by two very recent studies [44,45] and these preliminary data have to be confirmed by further studies.

■ Bipolar disorder

A recent trial found that the number of previous major affective episodes but not DUI was associated with lithium response in 100 bipolar patients [57]. A similar correlation between number of major affective episodes and lithium response with no effect of DI was found in 179 manic bipolar patients [58]. By contrast, in a sample of 35 resistant bipolar patients, treatment response to gabapentin was correlated with DI [59]. A previous trial found a significant correlation between DI and response to quetiapine in 145 psychotic patients (bipolar and schizophrenic) [60]. Finally, the results from a naturalistic study conducted by our group demonstrated that a longer DUI was associated with a higher number of suicide attempts and attempters in a sample of 320 bipolar patients [61].

In contrast to schizophrenia, DI but not DUI seems to be associated with poor treatment response in bipolar disorder. The data, however, are preliminary and further research is necessary.

■ Major depressive disorder & anxiety disorders

More data associated with bipolar disorder indicate DI and DUI as negatively correlated with treatment response in major depressed patients. Preliminary results indicated that patients with a DI of more than 2 years were less likely to respond to antidepressant and electroconvulsive therapy treatment in comparison with patients with a DI of up to 2 years [62]. In a recent trial, treatment response to escitalopram was found to be associated with a DI of less than 1 year in a sample of 2050 depressed elderly patients [63].

In a sample of 13 outpatients a correlation between DUI and treatment response/remission to fluvoxamine was found [64]. A total of 141 major depressed patients with a shorter duration of untreated episode showed a faster response to antidepressant treatment in comparison with patients presenting a longer duration of untreated episode [65]. In a trial conducted by our group, 68 patients affected by major depressive disorder and with a DUI of more than 1 year exhibited a higher number of recurrences under antidepressants compared with patients with a DUI of less than 2 years, indicating a poor response to long-term treatment [66].

Regarding anxiety disorders, preliminary data indicate a positive association between the length of DUI/DI and treatment response. In a naturalistic trial, 49 patients affected by panic disorder and with a long DI achieved treatment response with higher doses of imipramine in comparison with patients with a short DI [67]. In a trial conducted by our group, 96 patients affected by panic disorder had a higher probability of developing a subsequent major depressive disorder when presenting with a DUI of more than 1 year [68]. Data from three placebo-controlled multicenter trials showed that DI was a predictor of treatment response in patients affected by social anxiety disorder [69]. By contrast, in a more recent publication, a correlation between DI and treatment response in social phobia was not found [70]. A preliminary report indicated that response to venlafaxine was associated with a short DI in 32 patients with generalized anxiety disorder [71]. In another study, 100 patients with generalized anxiety disorder and a long DUI showed a more complicated course of illness, with high rates of comorbid psychiatric disorders with onset later than generalized anxiety disorder [72]. In two multicenter double-blind studies, treatment response to clomipramine in obsessive–compulsive patients was associated with a short DI [73]. These findings were confirmed by others [74]. Moreover, short DI predicted early response to antidepressants in OCD patients [75]. More recently it has been shown that a DUI of up to 24 months was predictive of treatment response in 66 OCD patients [76].

Major depressive and OCD patients seem to be less respondent to pharmacological treatment when showing a long DI/DUI. Preliminary data show similar results for DI and treatment response in patients affected by panic disorder, generalized anxiety disorder and social phobia.

No studies have investigated the relationship between DI/DUI and treatment response in post-traumatic stress disorder.

Conclusion

The majority of available data seem to show that a longer DI or DUI is associated with a reduced response to treatment in the different psychiatric disorders and, in the case of schizophrenia, to a worse outcome. The negative role of DI/DUI seems well established in schizophrenia, while data on mood and anxiety disorders should be considered as preliminary. In the case of bipolar disorder, for example, the number of major mood episodes instead of DI/DUI seems to be more relevant for predicting outcome of this clinical condition. The importance of these clinical variables on outcome of psychiatric disorders opens three interesting issues: the first is on the potential biological (and cognitive) factors responsible for the 'toxic' effect of DI/DUI; the second is represented by the clinical strategies to prevent a long DI/DUI [1]; and finally the third consists of the role of these variables in predicting outcome with possible implications on the treatment strategies of the nosographic guidelines.

The choice to review literature about DI/DUI across such a broad spectrum of psychiatric disorders is due to the importance of this clinical variable to predict outcome independently of the diagnosis. If the preliminary studies were focused on schizophrenia, recent literature would indicate DI/DUI as an important prognostic factor also for mood and anxiety disorders. The exact knowledge of the available data for DI/DUI, not only in schizophrenia, but also in mood and anxiety disorders, can help the clinician in the selection of the best treatment for patients.

Given that the relationship between a longer DUI and a worse outcome has been particularly stressed in the field of schizophrenia and first-episode psychosis, it is not surprising that the majority of interventions aim to reduce the latency to treatments in this specific area of mental disorders. Basically, early intervention has two main objectives: the first is to prevent the onset of schizophrenia in people with prodromal symptoms; and the second is to provide effective treatment to schizophrenics in the early stages of the illness, with the goal of reducing the severity of the illness [77].

Duration of untreated illness/DI have to be taken into account when explaining the discrepancy in efficacy of second-generation antipsychotics in schizophrenics. It is clear that, given the neurodegenerative process, patients with a longer DI/DUI show less sensitivity to the pharmacological activity of second-generation antipsychotics in comparison with patients with a shorter DI/DUI. Therefore, differences in the efficacy of second-generation antipsychotics versus neuroleptics are more difficult to detect in populations with long DI/DUI, where drug resistance associated with neurodegeneration is more likely [78].

In the field of affective disorders there has been great attention in terms of prevention programs in different populations. In particular, prevention programs subdivided into universal prevention, selective prevention and indicated prevention according to the presence of risk factors/soft symptoms, and basically represented by educational and psychological treatments, have been reviewed and grouped in meta-analyses with small but significant effect sizes, particularly in the short term [79–81].

Primary and secondary prevention are the only strategy that clinicians can use to prevent the brain damage related to a long DI/DUI. Future research has two main objectives: first, biological factors underlying the negative effects of DI/DUI on brain integrity have to be well investigated and established. Second, the role of pharmacotherapy on blocking neurodegeneration across psychiatric disorders has to be better defined. Preliminary data indicate that both antidepressants [82] and atypical antipsychotics [13] have a beneficial effect in preventing neurodegeneration correlated with a long DI/DUI. However, the effect size and differences between molecules in protecting patients from neurodegeneration still have to be established.

It is too early to envisage introduction of these variables in nosography (e.g., DSM-IV-TR or International Classification of Diseases) as specific predictors for outcome or for managing treatment strategies of evidence-based therapeutic guidelines. However, this article aims to stress this potentiality should be considered and research on these domains are mandatory to prevent or reduce drug resistance and ameliorate outcome in the different psychiatric disorders [83].

Finally, some limits of the studies mentioned in the present article have to be described. First, the studies investigating the relationship between DI and treatment response have the bias not to take into account the effects of previous

pharmacological treatments on brain structure. MRI studies showed that long-term treatment with typical antipsychotics produces an increase of basal ganglia volumes [84], lithium treatment in bipolar patients has a significant effect on brain structure, particularly in limbic/paralimbic regions [85], while antidepressants increase the hippocampus volumes [86]. Second, prospective neuroimaging studies have the limit to include only patients attending psychiatric services for the full length of the follow-up period.

Future perspective

Future research has the objective to investigate the reasons why DI/DUI have such a negative role on treatment response and outcome in different psychiatric conditions. DI/DUI are probably the clinical 'epiphenomenon' of common pathogenic factors among the different psychiatric disorders. Different hypotheses have been formulated about this issue. Neurodegenerative aspects certainly have an important role in explaining the poor treatment response in patients with DI/DUI as demonstrated by studies mentioned earlier. An alternative hypothesis is that patients with a long DUI/DI represent a subgroup with scarce insight and a more severe psychopathology that would justify a poorer response to pharmacological treatments. Finally, patients with a long DI/DUI could be genetically predisposed to chronicity or a more severe psychopathology with a delay of an adequate pharmacological treatment. Further neuroimaging, genetic and clinical studies will clarify the pathogenetic factors underlying DI/DUI and will direct clinicians to the best prevention strategies and treatment options.

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