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On the Cover:

ION ȚUCULESCU (1910-1962)

Copac în soare
Tree under the sun
“CLINICAL DEPRESSION” VS. “UNDERSTANDABLE SADNESS”: IS THE DIFFERENCE CLEAR, AND IS IT RELEVANT TO TREATMENT DECISIONS?

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One of the items of the “neo-kraepelinian credo”, articulated in the 1970s, was that “there is a boundary between the normal and the sick”. In other terms, it was maintained that there is a clear, qualitative distinction between persons who have a mental disorder and persons who have not (1). A corollary to this item was the statement that “depression, when carefully defined as a clinical entity, is qualitatively different from the mild episodes of sadness that everyone experiences at some point in his or her life” (1). Apparently in line with this statement was the observation that tricyclic antidepressants were active only in people who were clinically depressed; when administered to other people, they did not act as stimulant and did not alter their mood.

Today, the picture appears much less clear, and this is certainly in part a consequence of the evolution of psychiatric treatments. Guidelines for treatment of major depression often contain contradictory statements in this respect: on the one hand, the assertion that it is important to clearly differentiate clinical depression from normal adaptive responses to stress; on the other, the warning that antidepressant medications are effective even in the presence of significant life stress, and should not be withheld solely because the condition is understandable. These statements beget two questions: a) Are we really able to distinguish between a “dysfunctional” and an “adaptive” response to an adverse life event? b) Is this distinction clinically relevant, since treatment decisions are expected not to be influenced by whether the condition is understandable or not, but only by its clinical picture, severity, duration and by the degree of impairment of social functioning? These are questions with significant political, ethical, scientific and clinical implications, which have become particularly visible and pressing in the past few decades, in parallel to the escalation of the prevalence rates of depression in community studies, of the estimated social costs of depression, of the number of patients in treatment for depression, and of the prescriptions of antidepressant medications.

The National Comorbidity Survey, published in 1994, reported that the one-year prevalence of major depression in the US adult community was about 10%, and the lifetime prevalence about 17% (which means that 1 out of 10 Americans currently suffers from major depression and almost 1

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out of 5 has suffered from this disorder during his or her lifetime) (2). The World Health Organization estimated that depression will become by 2020 the second leading cause of worldwide disability, and is already the leading cause of disability for people aged from 15 to 44 years: these estimates were based on the above data on the prevalence of depression in the community and on a severity score according to which depression was placed in the second most severe category of illness, the same category as paraplegia and blindness (3). In the US, the number of patients with depression treated in outpatient settings increased by 300% between 1987 and 1997, the use of antidepressant medications among adults tripled between 1988 and 2000, and the spending for antidepressants increased by 600% during the 1990s (4).

This situation has generated concerns from both outside and within the psychiatric profession.

On the one hand, psychiatry has been accused to inappropriately medicalize ordinary life problems in order to expand the range of its jurisdiction. This criticism was well articulated in a book entitled “Making us crazy. DSM: the psychiatric bible and the creation of mental disorders” (5): “Determining when relatively common experiences such as sadness should be considered evidence of some disorder requires the setting of boundaries that are largely arbitrary, not scientific, unlike setting boundaries for what constitutes cancer or pneumonia”. “Rather than gaining any substantive understanding of your difficulties, you gain [from the DSM-IV] a far more interesting glimpse of psychiatry’s struggle to define its domain and expand its range”.

On the other hand, the above-mentioned prevalence rates of depression in the community have been regarded as unbelievable even from within the psychiatric profession: “Based on the high prevalence rates in both the ECA and the NCS, it is reasonable to hypothesize that some syndromes in the community represent transient homeostatic responses to internal or external stimuli that do not represent true psychopathologic disorders” (6); “The criteria diagnosed many individuals who were exhibiting normal reactions to a difficult environment as having a mental disorder” (7).

Particularly articulated has been the critique by Jerome Wakefield, an extensive version of which can be found in his book “The Loss of Sadness. How Psychiatry Transformed Normal Sorrow into Depressive Disorder” (4). The basic argument of this book is that the above-mentioned high prevalence rates of major depression, the WHO estimates about the social costs of this disorder, the high number of patients in treatment for depression and the increasing prescription of antidepressant medications are all consequences of the failure by DSM criteria to distinguish between true depression, a medical disorder which occurs despite there being no appropriate reason in the patient’s circumstances, and normal sadness, which represents a normal reaction to a major loss. What Wakefield proposes is either that the diagnosis of depression be “excluded if the sadness response is caused by a real loss that is proportional in magnitude to the intensity and duration of the response” or that the diagnosis of depression require that “despite there being no real recent loss
(or only losses of minor magnitude), the individual nonetheless experiences a sufficient number and intensity of symptoms” (8). Thus, the proposal is to extend the current exclusion criterion concerning bereavement to other major losses.

This approach may sound reasonable, but is of doubtful feasibility and reliability. In the community, it is almost the rule that major depression is preceded by an adverse event, as reported by the patient. Wakefield himself, in a recent study (9), found that as many as 94% of cases of single episode major depression had been preceded by a loss. An additional contextual criterion may exclude from treatment a substantial proportion of people in need of it. The decision on whether there is a causal relationship between the event and the response and on whether the response is proportional to the event is often difficult, and would be left to the subjective judgement of the clinician, with a high risk of low reliability (10). Even worse, the ideological orientation of the clinician may sometimes be decisive: there are psychiatrists who do believe that every psychopathological manifestation can be explained by looking at the individual’s environmental conditions. Moreover, even when confronted with the most severe life events, only a small minority of individuals develop major depression, raising the issue of what is meant by a “normal” reaction to stressors (11).

Actually, the point raised by Wakefield is not a new one. It was extensively explored by British psychiatry in the 1960s. In particular, Aubrey Lewis described in a classical paper his attempt to apply a set of criteria to distinguish contextual versus endogenous depression (12). He reported that: “The criteria were applied… But the more one knew about the patient, the harder this became. A very small group of nine cases emerged where… it could be said the situation had been an indispensable efficient cause for the attack… There was a small group of 10 in whom one could not in the least discover anything in their environment which could have been held responsible for the outbreak of the attacks. But all the others were understandable examples of the interaction of organism and environment, i.e., personality and situation; it was impossible to say which of the factors was decidedly preponderant”.

It is useful to report that, although Wakefield maintains that the distinction between depression and normal sadness has to be done on the basis of the context in which the symptoms occur, because there are no significant symptomatological differences between the two conditions, there are some studies suggesting that the two conditions may actually be qualitatively different. “Normal forms of negative mood such as despair or sadness must not be mistaken as depressed mood, characterized by a lack of holothymia and being an emotional feeling only known to depressed persons” (13). Along the same line, some studies carried out in patients with severe or chronic physical illness have described the differential features between clinical depression and understandable demoralization. A depressed person has lost the ability to experience pleasure generally, whereas a demoralized person is able to experience pleasure normally when he is distracted from thoughts concerning the demoralizing circumstance or event. The demoralized
person feels inhibited in action by not knowing what to do, feeling helpless and incompetent; the
depressed person has lost motivation and drive even when an appropriate direction of action is
known. Moreover, persons with clinical depression suffer from psychomotor, neurovegetative and
cognitive symptoms which are not typically present in demoralization (14).

However, the evidence provided by taxometric analyses of depression carried out in large
clinical samples suggests that major depression is not qualitatively distinguishable from less severe
mood states, although these analyses do not completely exclude the existence of a latent depression
taxon corresponding to “endogenous” or “nuclear” depression (15).

Another critical point concerning Wakefield’s approach is that the treatment implications of a
distinction between intense understandable sadness and non-contextual depression are currently
unclear. Actually, there are studies showing a high rate of response to antidepressant medication in
people who meet diagnostic criteria for a major depression episode during the first two months of
bereavement, which has led Zisook and his co-workers to conclude that even the current DSM-IV
exclusion criterion concerning bereavement may not be valid (so, rather than extended to other losses
as proposed by Wakefield, it should be eliminated) (16). Furthermore, some psychotherapeutic
techniques which have been proven to be effective in major depression, namely interpersonal
psychotherapies, are based on the assumption that the individual is currently experiencing problematic
environmental situations, of which the depressive condition is an understandable consequence.

In his book, Wakefield mentions the argument that treating intense understandable sadness
may disrupt normal coping processes and the use of informal support networks. In fact, it has been
repeatedly pointed out in the literature that externally elicited, mild to moderate, depressive states
may have an adaptive role that has developed through the evolution of the human species. They
may warn a person that past or ongoing strategies have failed and new strategies are needed.
Physiological slowing and social withdrawal may remove a person from high-cost, low-benefit
social interactions, and signalling one’s state to others may initiate others’ help without requiring
long-term payback. In this light, the experience of mental suffering is developmentally useful and
even necessary for human growth and self-actualization. By medicalizing this condition and treating
it with drugs we may undermine the coping strategies of the individual (17). The opposite view,
however, is that suffering in itself does not promote any growth and self-actualization, and that
what makes sense from an outside, universal philosophical perspective becomes unacceptable if we
try to say that the intense suffering of that particular person in real time and space ultimately exists
for his own good. In this light, the relief of severe mental suffering by appropriate, clinically sound
means becomes a legitimate medical purpose, exactly like the relief of severe physical pain (18).
This is, if you wish, the philosophical side of the problem. The clinical and scientific side is that the
effectiveness and cost-effectiveness of pharmacological and non-pharmacological interventions for
intense understandable sadness has to be proved by research.
One view which has been repeatedly expressed in recent years is that the boundary between mental disorders and normality can be decided only arbitrarily on pragmatic grounds (19). The boundary will be regarded as clinically valid if it has significant predictive implications in terms of response to treatment and clinical outcome. However, if prediction of treatment response is going to be one of our validating criteria in the case of the diagnosis of major depression, it is unlikely that the threshold for the diagnosis will be the same for all the various treatment modalities which are currently available. The threshold for response to an interpersonal psychotherapy, for instance, may be different from the threshold for response to an SSRI, which may be different from the threshold for response to a tricyclic antidepressant. This provides a rationale for the recent proposal of sequential stepwise treatment algorithms for people with depressive symptoms (20). Should we ignore the issue of the differential diagnosis between true depression and understandable sadness and simply apply one of these algorithms to all people presenting with depressive symptoms? In a community setting, this could be a reasonable response to the current state of affairs.

So, in conclusion, our initial questions, whether we are able to distinguish between a “dysfunctional” and an “adaptive” response to an adverse life event, and whether this distinction has significant treatment implications, remain without a clear answer at the moment. What we really need is further research evidence concerning the feasibility and reliability of the addition of a “contextual” criterion in the diagnosis of major depression, the clinical utility of this additional criterion in terms of prognosis and prediction of treatment response, and the biological correlates of non-contextual depression versus normal sadness, and probably also further research efforts aimed to operationalize that “distinct quality of mood” which may distinguish at least some forms of depression from normal sadness. The more these issues appear to be loaded with political and ethical implications, the more they require objective and convincing research evidence.

References


DIABETES AND THE RISK FOR COGNITIVE DECLINE AND DEMENTIA

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Abstract
Life expectancy is rising with increasing numbers of elderly people who develop dementia. In the absence of effective treatments for dementia, it is important to identify risk factors that are potentially modifiable, thus enabling development of treatment strategies that can prevent dementia, ameliorate its rate of deterioration or postpone its onset. Several cardiovascular risk factors such as type 2 diabetes, hypertension, cholesterol, and inflammation have been demonstrated in longitudinal epidemiological studies to increase risk of dementia, Alzheimer’s disease (AD), mild cognitive impairment (MCI), and cognitive decline. In this article, the association of diabetes with dementia and cognitive decline will be reviewed.

Key words: Alzheimer’s disease, cognitive decline, metabolic alterations.

Introduction
Alzheimer’s disease (AD) remains the most common cause of dementia in the elderly. The risk factors for AD, other than age, include female gender, family history, and at least one apolipoprotein E4 (APOE4) allele. In addition, cardiovascular risk factors, established as risk factors for vascular dementia, have also been associated with AD. These risk factors are of special interest since their potential for modification may affect the course of dementia. This paper reviews the most well established cardiovascular risk factor for dementia—diabetes, for which there is longitudinal epidemiological evidence of increased risk of dementia, Alzheimer’s disease (AD), mild cognitive impairment (MCI), and cognitive decline.

The association of diabetes with increased risk for dementia has been demonstrated relatively consistently, nevertheless, there is variability between studies which should be viewed in light of methodological differences between them; for example, differences in populations studied (age, gender, community or nursing home residence), duration of follow up, time at which diabetes was measured, (e.g. midlife vs. closer to ascertainment of dementia), proportions of people carrying diabetes, proportion of people being treated for diabetes, the methods by which the diabetes was measured (e.g.

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direct measure, self report, medical charts), in the confounders accounted for, and of course, in the outcome measures (typically AD, vascular dementia, all cause dementia, MCI, or cognitive decline).

**The association of diabetes and dementia, mild cognitive impairment and cognitive decline**

Type 2 diabetes has been demonstrated to increase risk for dementia in most\(^5,6\), but not all\(^8,9\) prospective epidemiological studies, with the highest odds ratios approaching 3-fold increased risk of dementia for diabetic individuals compared to non-diabetics\(^6\). Many studies have also shown increased risk for Alzheimer's disease (AD) and vascular dementia (VaD) (eg.\(^11\)). Recently, even pre-diabetes (defined as glucose >7.8mmol/l but <11.0 mmol/l) was associated with dementia (HR 1.77; 95% CI 1.02-3.12) and AD (HR 1.98; 1.12-3.50)\(^12\).

Diabetes\(^7\) as well as impaired fasting glucose, a pre-diabetic condition\(^14\), have also been demonstrated to be associated with increased risk for Mild Cognitive Impairment (MCI)\(^16\), a state of cognitive compromise considered to be a transitional phase between normal aging and dementia\(^17\).

Several studies have reported increased risk of cognitive decline in diabetes\(^19\). In a cohort of independent diabetic subjects, duration of diabetes and glycemic control (measured by HbA1c) were significantly associated with some cognitive dysfunction\(^20\). Higher hemoglobin A1c was also associated with lower cognitive function in primarily non-demented subjects of the ACCORD study\(^22\).

Diabetes has also been demonstrated by some\(^23,24\) but not all\(^27,28\) to be associated with faster cognitive decline in patients with incident AD\(^23\) and in non-demented subject\(^24\).

**Proposed Mechanisms**

Several mechanisms have been proposed for the association between diabetes and dementia: 1) diabetes is associated with micro and/or macrovascular disease\(^30\) which in turn increase the risk of cognitive decline and dementia\(^31,32\). Interestingly however, brain imaging studies have demonstrated conflicting results regarding the association of diabetes with cerebrovascular changes\(^33,34\). 2) Brain atrophy has been demonstrated relatively consistently in diabetic subjects, with some demonstrating an accelerating effect of greater hemoglobin A1c on brain atrophy rates\(^35\) while others demonstrated increased brain atrophy only in subjects with co-morbidity of diabetes and hypertension and not in subjects with either diabetes or hypertension alone\(^33,34\). 3) Another mechanism proposed for the association of diabetes with dementia and cognitive impairment is a defective insulin receptor signaling pathway (IRSP) in the central nervous system\(^40\); the IRSP is associated with vital brain processes including synaptic plasticity\(^41-43\), neuroprotection, neurodegeneration, survival, growth, energy metabolism, and longevity\(^45,46\). Insulin receptors (IR) are abundant throughout the brain\(^47\) and are expressed in especially high abundance in regions that support cognitive function\(^48\). Amyloid Beta (Aβ), the main component of neuritic plaques, hallmark...
lesions of AD, decreases insulin affinity and reduces the binding of insulin to its receptor\(^\text{50}\) preventing rapid activation of specific kinases required for multiple cellular functions, including long term potentiation (LTP)\(^\text{51}\). Soluble Aβ oligomers were recently shown to significantly lower IR responses to insulin and to cause rapid and substantial loss of neuronal surface IRs\(^\text{52}\). The IR desensitization found in AD brains\(^\text{53}\), hampers the release of Aβ from the intracellular to the extracellular compartment\(^\text{55}\), which may be a mechanism for its neurotoxicity\(^\text{56}\). 4) Advanced glycation end products (AGEs) may have a crucial role in the relationship between diabetes and dementia\(^\text{59-62}\). AGEs, which normally increase with age and faster with diabetes, are the products of naturally occurring reactions between reducing sugars, e.g. glucose, and free amine-containing proteins or lipids\(^\text{61}\). AD brains have significantly higher levels of AGEs than normal controls\(^\text{63}\) and in in-vitro studies, AGEs contribute to the formation of amyloid plaques and neurofibrillary tangles\(^\text{64, 65}\). 5) Insulin has been hypothesized to compete with Amyloid on its main degradative mechanism – the Insulin-Degrading Enzyme (IDE). Since IDE is much more selective for insulin than for Abeta, brain hyperinsulinism may deprive Abeta of its main clearance mechanism\(^\text{28, 67}\) 6) Finally, Hypoglycemia, a common complication of anti-diabetic treatments, has been demonstrated to increase risk for dementia (Whitmer et al. JAMA April 2009).

| Table 1. Risk of dementia, MCI and cognitive decline in patients with Type 2 diabetes |
|---------------------------------|---------------------------------|
| **Reference** | **Results (95% CI)** |
| **Dementia studies** | | |
| Schnaider Been\(^\text{2}\) | OR 2.8 (1.4-5.7) |
| Brayne\(^\text{4}\) | OR 2.6 (0.9-7.8) |
| Yaffe\(^\text{7}\) | OR 2.4 (0.9-6.1) |
| Ott\(^\text{10}\) | RR 1.9 (1.3-2.8) |
| Leibson\(^\text{13}\) | SMR 1.6 (1.3-2.0) |
| Whitmer\(^\text{15}\) | HR 1.5 (1.2-1.8) |
| Xu\(^\text{19}\) | HR 1.5 (1.1-2.1) |
| Peila\(^\text{21}\) | RR 1.5 (1.0-2.2) |
| Curb\(^\text{25,  26}\) | RR 1.4 (0.97-1.95) |
| MacKnight\(^\text{29}\) | RR 1.3 (0.9-1.7) |
| Hassing\(^\text{63, 65}\) | RR 1.2 (0.8-1.7) |
| **MCI studies** | | |
| Yaffe\(^\text{7}\) | OR 1.8 (1.1-2.8) |
| Luchsinger\(^\text{44}\) | HR 1.5 (1.0-2.3) |
| Luchsinger\(^\text{47}\) | HR 1.4 (1.0-1.9) |
| **Cognitive decline** | | |
| Gregg\(^\text{19,  54}\) | OR 1.7 (1.3-2.4) |
| Logroscino\(^\text{57, 58}\) | OR 1.3 (1.1-1.6) |
| Fontbonne\(^\text{38,  66}\) | OR >2 for 4 of 9 tests |
| Knopman\(^\text{56, 72}\) | 37% to 165% greater rate of cognitive decline in diabetics (depending on the test) |
| Okereke\(^\text{57, 58}\) | Diabetics decline faster; global cognition D-.09 (-.15, -.04) |
| Hassing\(^\text{73, 74}\) | Diabetics decline over twice as fast as non diabetics |
| Arvanitakis\(^\text{77, 78}\) | 44% greater rate of cognitive decline in diabetics |
| Hassing\(^\text{79, 77}\) | Diabetics decline twice as fast as non diabetics |
| Van den Berg\(^\text{80}\) | Diabetes was not associated with cognitive decline |

OR=odds ratio; RR=relative risk; HR=hazard ratio; SMR=standard morbidity ratio; D=difference rates
Hypoglycemic events may impair nutrient delivery to the brain, increase amount of glutamate, a neurotoxic neuro-transmitter, and down regulate markers of neuronal plasticity. Hypoglycemia may increase risk for vascular complications in the brain by inducing platelet aggregation and fibrinogen formation.

**Moderating Factors**

Diabetes is closely associated with other risk factors for dementia, such as age, hypertension, and the metabolic syndrome—a clustering of several commonly occurring disorders (including abdominal obesity, hypertriglyceridemia, low high-density lipoprotein (HDL) level, and hypertension). The combination of these risk factors, together with diabetes-specific characteristics (e.g. age of onset, glycemic control, use of anti-diabetes medications), demographic and socioeconomic factors, and genetic factors, might be important determinants of the increased risk of cognitive decline and dementia in individuals with diabetes.

Abdominal distribution of fat, an independent and potent risk factor for type II diabetes has been shown to be associated with increased risk for dementia. This association was independent of demographics, diabetes, cardiovascular comorbidities and body mass index (BMI). Insulin resistance, a consequence of central obesity, may be the mechanism by which central obesity affects cognition. Thus, this subset of pre-diabetic subjects may be possible candidates for early dementia prevention interventions.

The co-occurrence of diabetes and hypertension, has been demonstrated to significantly increase the risk of dementia and of cognitive decline. High systolic blood pressure interacted with borderline diabetes and with frank diabetes multiplying the risk of AD. Another modifying effect for the association of diabetes and dementia may be type of antidiabetic treatment: the risk for AD was doubled in diabetics compared to non diabetics in the Rotterdam study; however, within diabetics, those treated with insulin were at the highest risk (RR 4.3, 1.7-10.5) suggesting that more severe diabetes increases dementia risk. Consistent with these observations, subjects with longer duration of diabetes or with diabetes complications had steeper cognitive decline.

The mediating effect of other risk factors such as APOE4 genotype age on the association of diabetes with dementia has been less consistent. Participants with diabetes and the APOE4 allele had a risk ratio of 5.5 (CI 2.2-13.7) for AD compared with those with neither risk factors in the Honolulu Asia Aging Study and this was consistent with neuropathological findings. However, borderline diabetes was associated with AD only in non-APOE4 carriers in the Kongsholmen study. The effect of age on the relationships between diabetes and dementia is also difficult to interpret. The relationship between diabetes and dementia in the Framingham study was strongest for participants older than 75 but diabetes was not associated with accelerated cognitive decline in 85+ years of age.
participants in another study. This suggests that factors other than cardio-vascular risk factors (i.e. age, APOE genotype) interact with diabetes to increase the risk of cognitive compromise.

Inflammation is another potential mediator of the association of diabetes with cognitive decline and dementia. Inflammation is increased in diabetes and may have a role in diabetogenesis. Chronic hyperinsulinemia and obesity may both elicit chronic systemic inflammation. Although the main physiological abnormalities in type 2 diabetes are insulin resistance and impaired insulin secretion, the specific underlying determinants of these metabolic defects remain uncertain. An accumulating body of evidence suggests that inflammation may play a crucial intermediary role in pathogenesis of diabetes. Substantial experimental evidence suggests that interleukin-6 (IL-6) and C-reactive protein (CRP), two sensitive physiological markers of subclinical systemic inflammation, are associated with the development of hyperglycemia, insulin resistance, and overt diabetes. Several studies have demonstrated elevated levels of IL-6 and CRP among individuals both with features of the insulin resistance syndrome and with overt diabetes. These associations are often found after adjustment for obesity and cardiovascular disease, and even in non-obese individuals. Furthermore, a reinforcement cycle might exist since poor glycemic control is associated with increased inflammation. Improving glycemic control in turn, has been shown by some but not all to be associated with reduced inflammation.

There are several lines of evidence that support the importance of inflammation in the pathogenesis of cognitive impairment and AD. Acute-phase proteins, cytokines, chemokines, and their receptors are up-regulated in brains of AD patients. The abundance of activated microglia, the primary neuronal immune surveillance cell, is a relatively early pathogenic event in patients with AD. Proinflammatory cytokines augment amyloid precursor protein (APP)
Ramit Ravona-Springer et al.

and in turn, β amyloid (Aβ) induces further release of cytokines. Furthermore, gene polymorphisms of several inflammatory mediators have been associated with increased risk of AD. Blood elevations of inflammatory markers, specifically CRP and IL-6, have been shown to be risk factors for cognitive decline (generally assessed by a global cognition measure) and dementia. These epidemiological studies are consistent with the in vitro and in vivo studies suggesting a potential role of inflammation in the development of cognitive compromise.

Depression may be an additional modifier between diabetes and dementia. Diabetes is associated with 50-100% increased risk for depression, with severe symptoms of depression in approximately 30% of diabetic subjects. It is unknown whether diabetes, through cerebro-vascular complications, causes depression, or whether depression itself or antidepressant medications induce diabetes. Depression is associated with worse glycemic control and increased risk for diabetes related complications, potentially affecting cognition. Depression per se is also a risk factor for dementia. Future studies should assess optimal cognitive screening strategies and optimal antidepressant treatments in depressed diabetic patients.

Effects of anti-diabetic treatments on cognition

Interestingly, results of preclinical as well as clinical studies using antidiabetic treatments, have demonstrated potential efficacy on cognitive compromise. Rosiglitazone treatment of Tg2576 mice (transgenic mice over-expressing amyloid precursor protein) resulted in better spatial learning and memory abilities and an approximately 25% reduction in Aβ42 levels. In a double blind study in older diabetic adults randomized to Roziglytazone or glyburide treatment as add on treatments to metformin, achievement of better glycemic control was associated with improved cognitive performance. Rosiglitazone therapy resulted in improved memory and selective attention while not affecting glucose levels in a study of 30 AD or MCI non-diabetic subjects during a period of 6 months. A trial with 518 mild to moderate AD patients treated with rosiglitazone for six months reported significant improvement in cognition only in patients who did not possess an APOE4 allele. Craft et al. performed several investigations examining the effect of intravenous insulin in non-diabetic elderly adults with AD. Mild to moderate AD patients’ immediate and delayed recall were improved in hyperglycemic and hyperinsulinemic conditions compared to a saline control condition. However, normal controls had no change in their cognition. Intranasal insulin administration has recently shown some promising effects on memory. Substantially reduced neuritic plaques (NPs), the hallmark lesions of the AD brain, were found in the brains of diabetic subjects who during life received a combination of insulin and another anti-diabetic medication. Recently, the SALSA study reported decreased rates of cognitive decline in diabetic subjects receiving anti-diabetic medications (insulin or oral hypoglycemic) compared to untreated diabetic subjects.
These studies are encouraging, especially in light of the beneficial effect of diabetes control on non-cognitive complications of diabetes. Nevertheless, they are not sufficient to draw conclusions. In a recent search of the literature by the Cochrane control trial register, no appropriate studies were found for meta-analysis regarding the effect of treatment for type 2 diabetes and degree of metabolic control on the development of dementia. Many questions should be answered prior to implementation of antidiabetic treatments as strategies for dementia prevention; for example, at what stage/ severity of diabetes should treatment be initiated? What degree of glycemic control should be aimed for? What medications should be used? Should treatment strategies change with patients' age? Etc. The importance of these questions is stressed by evidences showing that severe hypoglycemic episodes, which are complications of antidiabetic treatments, are associated with cognitive decline in older subjects with type II diabetes. Additionally, very strict diabetes control has been demonstrated to increase mortality. Increased myocardial infarction and death from cardiovascular causes were reported in rosiglitazone users.

**Conclusions**

Diabetes and pre-diabetic states are risk factors for cognitive decline and dementia and may increase rate of dementia deterioration. As these are potentially modifiable risk factors, their treatment may serve as a strategy for dementia prevention or postponement. Several mechanisms and modifying factors may be involved in this association, suggesting pathways for interventions. As diabetes is a heterogeneous disease, further studies should detect diabetic subjects at increased risk for cognitive impairment, optimal screening tools and optimal intervention strategies.

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HOMOCYSTEINE – BIOMARKER IN NEUROPSYCHIATRIC DISORDERS

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Abstract
Hyperhomocysteinemia has an important role in the pathogenesis of some neuropsychiatric diseases, some studies suggest that homocysteine is a biological marker of neurodegeneration, and its level may accelerate the progression of the neurodegenerative disorders. Associations between homocysteine concentration and the severity of extrapyramidal effects at patients treated with antipsychotics, given findings linking homocysteine to dopamine-mediated toxicity or between the level of homocysteine and the degree of brain atrophy at patients with schizophrenia, having in mind the fact that the polymorphisms of the MTHFR gene determine high levels of homocysteine that affects NMDA glutamatergic systems and produces DNA breakage and apoptosis in the cell brain followed by brain atrophy sustain the idea that homocysteine is a biomarker for neuropsychiatric diseases and its measurement could be used as a way of monitoring the response to therapy or, in some cases, as a predictor to the severity of adverse effects of the therapy. Other studies consider that homocysteine is just a risk factor for a variety of central nervous system diseases including Alzheimer disease, schizophrenia, cognitive impairment in the elderly, neuroleptic-induced movement disorders, including tardive Parkinsonism and tardive dyskinesia, other movement disorders such as idiopathic Parkinson's disease, Huntington's disease and primary dystonia.

Key words: homocysteine, neuropsychiatric diseases, vitamin B12.

Introduction
Homocysteine can be a biomarker for neuropsychiatric diseases and its measurement could be used as a way of monitoring the response to therapy or, in some cases, as a predictor to the severity of adverse effects of the therapy, or its high level is just a risk factor for a variety of central nervous system diseases including Alzheimer disease, schizophrenia, cognitive impairment in the elderly, neuroleptic-induced movement disorders, including tardive parkinsonism and tardive dyskinesia, other movement disorders such as idiopathic Parkinson's disease, Huntington's disease and primary dystonia. Elevated plasma levels of homocysteine are also proved to be a risk factor for systemic vascular diseases, stroke and vascular dementia.

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Metabolism

Homocysteine is a sulphur-containing amino acid that is closely related to methionine and cysteine. It cannot be obtained from food and it is the result of the methylation cycle. In human cells, homocysteine is formed by the demethylation of the essential amino acid methionine and an abnormality in the methylation pathway may have a role in the pathogenesis of schizophrenia.

Three enzymes are directly involved in the homocysteine metabolism: methionine synthase, betaine homocysteine methyltransferase, and cystathionine β-synthase. Several other enzymes are indirectly involved. Vitamins B6 and B12 are cofactors to these enzymes and folate is a substrate in the methionine synthase-mediated reaction. Methionine is converted by methionine-adenosyltransferase into S-adenosylmethionine that is the most important methyl donor in humans, and donates its methyl group in numerous transmethylation reactions, such as methylation of DNA, RNA, proteins and lipids, hormones and neurotransmitters. These transmethylation reactions, catalyzed by methyltransferases, form S-adenosylhomocysteine, which is an inhibitor of many methyltransferases, such as catechol-O-methyltransferase (COMT). In its turn, S-adenosylhomocysteine hydrolyses to adenosine and homocysteine. Homocysteine can then be metabolised via three metabolic pathways that function to maintain low intracellular concentrations of homocysteine. Firstly, homocysteine can be remethylated to methionine via the enzyme methionine synthase (MTR), which uses vitamin B12 as co-factor. In this remethylation reaction 5-methylthetrahydrofolate donates its methyl group to vitamin B12, which, in its turn, transfers it to homocysteine to form methionine and tetrahydrofolate.

Folate is obtained via the diet and is reduced via several steps involving enzymes such as serine-hydroxymethyltransferase and methylenetetrahydrofolate reductase (MTHFR) into 5-methyltetrahydrofolate, the predominant form of folate in plasma (1). Secondly, in the liver and kidney homocysteine can also be remethylated into dimethylglycine by the enzyme betaine-homocysteine methyltransferase with betaine as methyl donor. Thirdly, intracellular homocysteine can be irreversibly degraded to cysteine through the transsulphuration pathway that is mainly limited to cells of the liver and kidneys. Vitamin B6 dependent cystathionine β-synthase has an important role in this reaction. As betaine-homocysteine methyltransferase and cystathionine β-synthase are absent in central nervous tissue, 5-methyltetrahydrofolate is the only methyl donor involved in the methylation of homocysteine in central nervous tissue.

Causes of hyperhomocysteinemia

Disturbances in this metabolism, caused by a genetic enzyme defect (polymorphisms of the MTHFR gene) or by deficiency of cofactors (vitamin B12, vitamins B6, folat, vitamin B2), normally result in cellular accumulation of homocysteine, and secondary causes hyperhomocysteinemia.
Hyperhomocysteinemia is frequently associated with low levels of folate, vitamin B12 and B6. Moderate elevations of homocysteine may often be caused by one or more unhealthy lifestyle factors that influence vitamin metabolism, such as smoking, high alcohol consumption, low nutritional intake of vitamins, high coffee consume and lack of physical exercise. Increased homocysteine plasma levels seem to have an important role at patients with these basal ganglia disturbances, by exerting neurotoxic effects, contributing to neurotransmitter imbalance in motor circuits, and increasing the risk for vascular insults and cognitive dysfunctions.

Increased homocysteine plasma levels seem to have an important role at patients with these basal ganglia disturbances, by exerting neurotoxic effects, contributing to neurotransmitter imbalance in motor circuits, and increasing the risk for vascular insults and cognitive dysfunctions.

The most commonly toxic mechanisms of homocysteine is oxidative injury realized by different mechanisms such as abnormalities in folate metabolism or excitotoxic effects mediated by N-methyl-D-aspartate (NMDA) glutamate subreceptors that could also oxidize membrane lipids and proteins and determine abnormal methylation, damaged DNA synthesis/repair. The vascular effect of homocysteine is very important. And it is caused by direct damage to endothelial cells, increased platelet activity, pro-coagulant effects, increased collagen synthesis, and enhanced proliferation of smooth muscle cells.

Oxidative stress may induce various vascular and neurological damages, and seem to play a major role in aging and neurodegenerative disorders such as Alzheimer disease and Huntington’s disease, amyotrophic lateral sclerosis, Parkinson’s disease. Elevated homocysteine and nitrite (a metabolite of NO) levels were found in multiple sclerosis patients, in both L-dopa-treated and non-treated Parkinson disease patients and in patients with cerebrovascular disorders.

Oxidation of homocysteine leads to the formation of homocysteine sulphinic acid and homocysteic acid, both shown to have potent excitotoxic effects on different subtypes of N-methyl-D-aspartate (NMDA) glutamate receptors (2, 3). Homocysteine is an endogenous glutamate receptor agonist, and is proved to act on N-methyl-d-aspartate (NMDA) receptor subtype. An interaction between excitotoxic NMDA activity and NO-related oxidative damage has been proposed in aging, neurodegenerative disease, and other neurological disorders (4, 5). Homocysteic acid and cysteine sulphinic acid can activate NO formation by interaction with the NMDA receptors. This has also been associated with homocysteine-related neurological damage (6).

**Homocysteine and neuropsychiatric diseases**

Recent studies showed a positive correlation between the levels of homocysteine and the severity of the symptoms from different neuropsychiatric diseases such as the following: Alzheimer disease, schizophrenia, neuroleptic-induced movement disorders, including tardive parkinsonism
and tardive dyskinesia, other movement disorders such as idiopathic Parkinson's disease, Huntington's disease and primary dystonia.

Hogervorst et al. (2002) showed a significant negative association between homocysteine and minimal hippocampal width, and also a significant positive association between homocysteine and cerebral infarction, white matter changes, and degree of atrophy at patients with Alzheimer disease (7). Elevated homocysteine levels in schizophrenics in connection with the C677T polymorphism of the MTHFR gene and low folate status are described (8). Homocysteine affects NMDA glutamatergic systems (9), and seems to play some role in the pathogenesis of schizophrenia. Homocysteine may enhance oxidative stress processes (10) that also may be a risk factor for schizophrenia.

Homocysteine was also suggested to induce DNA strand breakage and apoptosis (11) and some authors suggested a link between apoptotic processes and schizophrenia (12). High homocysteine levels are accompanied by high S-adenosyl-homocysteine levels. Elevation of S-adenosyl-homocysteine was suggested to be associated with DNA hypomethylation and alterations in gene expression (13). Altered gene expression may be associated with the pathogenesis of schizophrenia. Significantly elevated plasma levels of homocysteine have been reported in patients with Parkinson’s disease (PD) (13, 14).

In one study the levels of homocysteine were elevated by 60% in levodopa-treated patients with a marked elevation occurring in patients with the MTHFR 677TT genotype. The homocysteine and folate levels were inversely correlated in this group (13). Additional data from this group and other recently reported data firmly support that this polymorphism is a significant factor for hyperhomocysteinemia in L-dopa-treated patients.

Homocysteine monitoring may be of particular value for Parkinson disease as it is neurotoxic to the nigrostriatal dopaminergic system. Because of the neurotoxicity nature of homocysteine to dopaminergic neurons there was suggested that elevated level of this molecule in patients with Parkinsonism may lead to accelerate the progression of the disease. Hyperhomocysteinemia in Parkinson disease could be explain by levodopa administration and it may be implicated in the development of motor complications and non-motor symptoms, such as dementia.

Hyperhomocysteinemia has been evidenced in Huntington disease and dystonic patients (14). High serum total homocysteine level may constitute a risk factor for certain variants of neuroleptic-induced movement disorder especially in young schizophrenic or schizo-affective male patients and studies have been made in these direction (15).
Conclusions

Hyperhomocysteinemia has an important role in the pathogenesis of some neuropsychiatric diseases, some authors consider that homocysteine is a biological marker of neurodegeneration, and its level may accelerate the progression of the neurodegenerative disorders.

It is possible a correlation between the level of homocysteine and the degree of brain atrophy at patients with schizophrenia, having in mind the fact that the polymorphisms of the MTHFR gene determine high levels of homocysteine that affects NMDA glutamatergic systems, and produces DNA breakage and apoptosis in the cell brain followed by brain atrophy.

References


LONG-ACTING RISPERIDONE INJECTION – A PATH TO REMISSION IN SCHIZOPHRENIA
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Abstract
Aim. The clinical efficacy, adverse effects, cost, and dosage of long-acting risperidone injection are reviewed.
Summary. Risperidone is the first atypical antipsychotic available in a long-acting injectable formulation. After a single injection, significant plasma levels of the drug are achieved at week 3 and sustained through week 6. Our review demonstrates the efficacy, safety, and tolerability of long-acting risperidone injection in patients with schizophrenia. According to the reviewed data, risperidone injection was well tolerated, with low adverse-effect rates. Weight gain with long-acting risperidone injection was insignificant. Extrapyramidal symptom ratings are comparable with other novel antipsychotics.
Conclusion. With its tolerability and efficacy, long-acting risperidone injection has the potential to extend the benefits of antipsychotic medication in patients with schizophrenia, achieving the remission criteria with a good economic imbalance.
Key words: schizophrenia, antipsychotics.

Introduction
Schizophrenia is a chronic, severe and disabling brain disorder that seriously impairs a person’s ability to think clearly, relate to others and to function productively in society. Schizophrenia typically develops in adolescence or the early 20s, although symptoms may not become obvious until later life (33). While most males first become ill between the ages of 16 and 25, the majority of females develop symptoms between ages 23 and 36 (1). Schizophrenia is marked by ‘positive’ and ‘negative’ symptoms, characterized by psychotic episodes. When symptoms worsen, these episodes often recur which is known as a relapse. The severity and regularity of these episodes vary from person to person. Each successive relapse will often become worse over time and harder to control. After several relapses, the patient’s overall condition can deteriorate to such an extent that he/she may not be able to reach the same level of health and functioning they had before becoming ill, as the graph below demonstrates. In addition, during

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these relapses, patients have an increased risk of hospitalization. The disruption caused by a relapse can be devastating for a patient and their family.

**Socio-economic impact of schizophrenia**

Approximately 25 percent of people with schizophrenia will recover after one psychotic episode. However, for many, schizophrenia is a life-long illness and a severe burden to both the patient and their family and friends. Many patients will be out of work as a result of the illness, and it may also seriously impact on their relationships and social life. Moreover, people with schizophrenia will often be in poor physical health and they are more likely to eat poorly, smoke and drink alcohol to excess. Family life is also disrupted as on average carers spend 15 hours a week looking after a family member with schizophrenia.

**Treatment challenges in schizophrenia**

While there is no real cure for schizophrenia, the psychiatrist has to manage the appropriate treatment, particularly when intervention is sought and received early in the illness. According to the United States’ National Alliance for the Mentally Ill (NAMI), the current treatment-success rate for schizophrenia is about 60 percent, compared to just 41-52 percent for patients with heart disease (37). However, recovery to the maximum extent possible depends on maintenance of treatment. Data show that about 75 percent of people with schizophrenia relapse within a year to 18 months if antipsychotic drug therapy is stopped or taken inconsistently (32, 23). Unfortunately, it is estimated that as few as 25 percent of people with schizophrenia take their medication on a continuous, consistent basis (11).

**Improving compliance**

When patients stop taking their medication it is likely that their symptoms may return. These relapses can result in serious problems and hospitalization. Non-compliance to medication is among the most common causes of relapse in schizophrenia (16), and relapse rates are up to four times higher in patients who are non-adherent to their medication (15). Non-adherence to medication is actually the most important factor related to readmission of the patient in the hospital.

Patients who relapse can take over a year to return to their pre-relapse level of social functioning (12), and with each successive relapse, the person’s condition may deteriorate and previous levels of health and functioning may not be reached again (18).

One potential aid in addressing these challenges is long-acting injectable antipsychotic that require less frequent administration and facilitate regular interchange with a physician or other healthcare professional.
While replacing daily pills with long-acting injections isn’t a perfect and unique solution for treatment non-adherence, unlike pills or liquids that are taken privately, a missed appointment for an injection is often evident to the family or carers. This can help the social supporting group and the therapeutic team to identify any problems the patient may have with their treatment regimen and provide the individual with the appropriate follow-up in an effective time frame.

The introduction in the 1960s of long-acting, intra-muscular injections of older, conventional antipsychotics or so called “depot” formulations was specifically intended to address the problem of non-adherence. Many studies show that patients prefer long-acting injections to oral treatment (40). However, the incidence of movement-related side effects is a significant disadvantage of these older formulations. A further drawback is that, because the older injections are typically oil-based, they are often associated with pain and/or irritation (28).

The next generation of long-acting injections combine the advantages of the newer generation antipsychotics with the benefits of a long-acting formulation, which are less painful to receive. These medications may help to improve symptoms and adherence which may lead to reduced relapse rates, hospitalization and improve quality of life (33).

**Pharmacology**

Long-acting risperidone is a suspension administered by intramuscular injection in the upper-outer gluteal area. It consists of risperidone impregnated in microspheres composed of a biodegradable, high-molecular-weight, glycolic acid-lactic acid (polyactide-glycolide) matrix (39). The long-acting risperidone powder requires refrigeration at 2-8 °C. However, the vial is stable for up to seven days at 25 °C or below (17). Since the suspension is not uniform and the syringe is ungraduated, it is not possible to accurately inject a partial dose in order to reduce the dose given.

**Clinical Efficacy**

Several studies have been conducted to evaluate the efficacy and safety of long-acting risperidone in patients with schizophrenia or schizoaffective disorder (22,7,13). In a 12-week, double-blind, placebo-controlled U.S. trial, Kane et al. (22) used the PANSS and the Clinical Global Impressions scale (CGI) to assess efficacy in 400 outpatients and inpatients with schizophrenia. The PANSS is a 30-item scale with ratings of 1-7; the CGI also uses ratings of 1-7 to rate overall severity of illness. The mean baseline PANSS score for subjects was 82, and the mean age was 38 years. Significant improvements in positive symptoms (such as delusions and hallucinations), negative symptoms (such as blunted affect and social withdrawal), total PANSS scores, and CGI ratings were produced by all three doses of long-acting risperidone injection evaluated (25, 50, and 75 mg) administered every two weeks. Regardless of the baseline severity of illness, improvements were greater in the subjects receiving 25 or 50 mg than in those receiving 75 mg. This suggests that there is
no added benefit from the 75-mg dose. Clinical improvement at the end of the study (≥20% reduction in total PANSS scores) was seen in 17% of placebo recipients and 47%, 48%, and 39% of subjects in the 25-, 50-, and 75-mg risperidone groups, respectively (p < 0.001).

A further analysis of this 12-week trial focused on patients who received oral olanzapine prior to the initiation of therapy with long-acting risperidone injection (19). Compared with baseline, these patients demonstrated significant improvement in total PANSS scores (p = 0.03), positive symptoms (p < 0.05), negative symptoms (p < 0.05), and anxiety and depression (p < 0.05) when they were switched to the risperidone formulation.

Chue et al. (7) conducted a randomized, double-blind, 12-week trial in 640 patients to establish whether long-acting risperidone injection was as effective as oral risperidone. After stabilization on oral medication for 8 weeks, the subjects were randomly assigned to receive either (1) oral risperidone and placebo injection or (2) long-acting risperidone injection and oral placebo and monitored for 12 weeks. Patients receiving long-acting risperidone injection every two weeks also received three weeks of active oral medication following the first injection. The study was completed by 84% of those given oral medication and 80% of those who received risperidone injection. Significant improvements from baseline to the end of the study in total PANSS scores, positive symptoms, negative symptoms, disorganized thoughts, and anxiety and depression were seen in both groups (p < 0.05). Non-inferiority testing further demonstrated that the injectable formulation was not inferior to oral risperidone and that subjects could be switched to it without loss of efficacy.

Fleischhacker et al. (13) conducted an international one-year open-label trial in 615 patients with schizophrenia. The mean PANSS score was 66, and the mean age was 42 years. Compared with baseline, patients receiving long-acting risperidone injection every two weeks at all doses had improvements in total PANSS scores (p < 0.01), positive symptoms (p < 0.01), and negative symptoms (p < 0.001) at the end of the study. Since the subjects were considered stable at baseline, these improvements are especially noteworthy. Clinical improvement, defined as a reduction in total PANSS scores of at least 20%, was seen in 49% of the risperidone recipients. Furthermore, 34% and 18% of these patients achieved >40% and >60% reductions in total PANSS scores, respectively, after one year of treatment (29). As in the Kane et al. (22) trial, subjects in this one-year study receiving 25 or 50 mg of long-acting risperidone injection had greater improvement than those given 75 mg.

A number of subanalyses of the data from the study by Fleischhacker et al. (13) were conducted. One looked at the effect of prior antipsychotic therapy on the efficacy of long-acting risperidone (42). Patients who had previously been treated with oral risperidone accounted for approximately 50% of the population studied, while approximately 25% had received “depot” conventional antipsychotic agents. Eighteen percent, 33%, and 10% of the patients whose illness
had been stable on oral risperidone, “depot” conventional antipsychotics, and oral conventional antipsychotics, respectively, showed more than 60% improvement in PANSS scores when they were switched to long-acting risperidone (27,14,34,35).

Analysis of a further 110 patients with schizoaffective disorder who had participated in the Fleischhacker et al. (13) study found that they had benefited significantly from long-acting risperidone (20). Total PANSS scores improved by a mean ± S.D. of 9.0 ± 1.6 points between baseline and the end of the study (p < 0.001). Clinical improvement -- measured as ≥20%, 40%, or 60% reduction in total PANSS scores from baseline -- occurred in 58%, 39%, and 18% of the subjects, respectively.

**The definition of remission**

The exact definition of the word ‘remission’ is ‘the state of absence of disease activity in patients with a chronic illness. Remission of symptoms is not a new concept, and definitions of remission criteria currently exist for both psychiatric and non-psychiatric illnesses. However, in psychiatric illnesses remission is usually defined by a low level of symptoms with mild disability.

The concept of remission in schizophrenia begins to move the somewhat negative perception of being ill to the much more positive assertion of being well. At the simplest level, the concept begins to accept the idea that patients can have periods of time when they are well and although the condition can fluctuate, the possibility of long-term recovery is very real.

An important part of remission in schizophrenia is the improved quality of life it gives patients and the proposal that ‘symptomatic remission is an achievable objective for a significant proportion of patients with a diagnosis of this illness (9). With the advances in medication, remission is now considered to be clinically relevant in the treatment of schizophrenia, where patients are able to progress beyond stability (26).

**The development of the concept of remission**

Unfortunately, schizophrenia is a somewhat stigmatised condition, which is mainly attributed to a lack of knowledge, and for many years it has been regarded as a disease with little or no hope of recovery. In fact, dramatic improvement in people diagnosed with schizophrenia was regarded by many clinicians as evidence of an original misdiagnosis.

However, this view has altered over time due to advances in knowledge, improvements in psychotherapeutic techniques and the introduction of antipsychotic medications.

Due to advancements in the understanding of schizophrenia, the treatment goals have evolved significantly. The diagram below illustrates how these objectives have evolved over time,
for example, before the 1960s, the treatment goal was to improve self-care, reduce aggression and reduce self-injury. However, by 2000 this goal had changed to focus on improving a patients’ ability to function within society and the potential for remission.

**A consensus for remission in schizophrenia**

In April 2003, an international remission expert group convened to develop a consensus definition of remission as applied to schizophrenia. The consensus aimed at developing a criterion for sustained symptomatic remission in patients with schizophrenia, similar to the remission consensus developed in mood and anxiety disorder (34). Sustained remission was defined by using an absolute threshold of severity of the diagnostic symptoms of schizophrenia and a duration component.

The need for a consensus came about due to a growing understanding of the disease course and advancements in treatment options, including oral and long-acting injectable atypical medications.

The working group established that the remission criteria for schizophrenia needed to be an attainable clinical goal that was easily measurable. It needed to employ a time component and support alignment of the views of patients, caregivers and clinicians.

The Positive and Negative Syndrome Scale (PANNS) consists of eight specific items reflecting all three dimensions and core symptoms of the illness, all of which were selected by the working group as a criterion for remission in schizophrenia. In order to achieve symptomatic remission, patients would need to score mild or less simultaneously on all of the eight core symptoms and maintain this score for a minimum of six months.

According to the consensus, a patient can be considered in remission when during a period of at least six months; all of the core symptoms are either absent, minimal or mild enough so as not to interfere with the patient’s day to day life (34).
Core symptoms:
- Delusions
- Conceptual disorganisation
- Hallucinatory behaviour
- Unusual thought content
- Mannerisms and posturing
- Blunted affect
- Social withdrawal
- Lack of spontaneity or flow of conversation

The table below highlights both the advantages of having clearly defined remission criteria and the benefits of achieving remission for patients, carers and psychiatrists.

<table>
<thead>
<tr>
<th>ADVANTAGES OF A CLEARLY DEFINED REMISSION CRITERIA</th>
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| PATIENTS AND CARERS: | Patients have clear expectations of what is achievable in the long-term and challenge their treatment expectations ‘beyond stability’
| | Patients and carers are better enabled to communicate long-term goals to psychiatrists
| PSYCHIATRISTS: | Provides clinicians with a robust, well-defined and achievable outcome goal in the long-term treatment of schizophrenia
| | Helps to facilitate comparisons of effectiveness across the range of available therapeutic options and clinical trials
| | They can help patients reach sustained remission

<table>
<thead>
<tr>
<th>ADVANTAGES OF ACHIEVING SUSTAINED REMISSION</th>
</tr>
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| PATIENTS & CARERS: | There is a reduced burden on the carers
| | Patients improve in their overall daily living…
| | Personal hygiene
| | Domestic activities
| | Managing finances
| | Daily activities/work
| | Executive functioning
| | Improved cognitive ability
| | Vigilance
| | Working memory
| | Long-term memory

Obstacles in remission: adherence to treatment

Although remission is an achievable goal in the treatment of schizophrenia, it is important to recognise the obstacles that can delay the patient in reaching this goal. There are at least two major obstacles in achieving continuous improvement in patients with schizophrenia.

The first obstacle is ensuring patient adherence with medication. Patients who fail to take their prescribed medication will reduce the effectiveness of their treatment and this will contribute to the worsening of their condition, possible deficits in cognition and psychosocial functioning, and ultimately relapse. This can cause further problems as research has shown that patients not in remission have a reduced cognitive ability and consequently experience difficulty complying with their treatment.
The second obstacle is treatment efficacy and tolerability. It is important to ensure that the medication prescribed to the patient is effective and well-tolerated.

**Safety and Tolerability**

Long-acting risperidone injection is generally well tolerated and has an adverse-effect profile similar to that of oral risperidone. In the Kane et al. (22) trial, similar proportions of individuals receiving long-acting injection and placebo reported adverse events. The rate of serious adverse effects was 23.5% in the placebo group and 13%, 14%, and 15% in the risperidone 25-, 50-, and 75-mg groups, respectively. Serious adverse effects were defined as those that resulted in death or were life threatening, required hospitalization or prolonged hospitalization with persistent or significant disability, or resulted in incapacity, congenital anomaly, or a birth defect (22). Overall, the rate of patient withdrawal from the study because of adverse effects was 12% in the placebo group and 11-14% in the risperidone recipients. The most frequently reported adverse effects were headache, agitation, psychosis, insomnia, and anxiety.

Long-acting risperidone injection was also well tolerated in the trial by Fleischhacker et al. (13); two thirds of the patients completed the study, and less than 6% of any of the treatment groups withdrew because of adverse effects. The percentage of patients with adverse effects declined from 68% in the first three months of the study to 43% in the last three months, with the most frequently reported problems being anxiety (24%), insomnia (21%), psychosis (17%), and depression (15%).

Because of their activities as D₂-receptor antagonists, EPSs are a potential concern with all atypical antipsychotics. Both Kane et al. (22) and Fleischhacker et al. (13) used the 55-item Extrapyramidal Symptom Rating Scale (ESRS) to evaluate the severity of EPSs. This scale assesses the objective frequency, objective severity, and subjective severity of parkinsonism, dyskinesia, akathisia, and dystonia (5).

In both the 12-week Kane et al. (22) and one-year Fleischhacker et al. (13) trials, baseline ESRS scores were low. EPS severity decreased in all groups during the Kane et al. trial, with the greatest improvement observed in the 25-mg long-acting risperidone group. After completion of the concomitant oral treatment phase (the first three weeks after the first injection of long-acting risperidone), the EPS rate was 9% in those receiving placebo and 3% in those receiving risperidone 25 mg. The rates for the 50- and 75-mg doses were 14% and 23%, respectively. In the Fleischhacker et al. study, according both to patients’ subjective ratings and physicians' ratings, the severity of movement disorders was low at baseline and improved significantly during treatment with long-acting risperidone injection. Patients previously treated with oral risperidone and those who had previously received depot conventional agents both had significant improvements in movement disorders at week 50, as determined by the subjective and objective ratings on the ESRS.
Long-Acting Risperidone Injection – A Path to Remission in Schizophrenia

(p <0.05) (14,37). Treatment-emergent tardive dyskinesia occurred in only 0.68% of patients in the one-year trial by Fleischhacker et al., while 28.4% of the patients diagnosed with dyskinesia at baseline (n = 102) improved significantly after treatment with long-acting risperidone (4).

Other important adverse effects of atypical antipsychotic agents include increases in body weight (8), glucose intolerance (25), and prolactin elevation (2, 3). Body-weight changes by the end of the 12-week trial by Kane et al. (22) were small (gains of 0.05, 1.2, and 1.9 kg in the 25-, 50-, and 75-mg groups, respectively), while the mean weight change in the placebo group was a loss of 1.4 kg. Weight gain in the one-year study by Fleischhacker et al. (13) was 1.7, 2.6, and 1.9 kg in the 25-, 50-, and 75-mg groups, respectively. This could indicate that the weight gain occurs early in treatment but does not increase dramatically with continued use. Glucose levels were not specifically reported, but there were no clinically significant changes from baseline in the one-year trial (13).

Additional clinical assessments during treatment with long-acting risperidone injection included electrocardiograms to assess cardiovascular safety. No significant differences in cardiovascular function between risperidone and placebo, or detrimental effects of long-term treatment, were observed, including in patients 65 years of age or older (22,13,36).

Cost Benefit Considerations

The duration and frequency of hospitalization can markedly affect the cost of treating a patient with psychosis. Hospitalization is the largest component of the direct cost of treating schizophrenia (24). Chue and colleagues (6) evaluated rehospitalization rates in 397 patients with stable schizophrenia or schizoaffective disorder who were treated with long-acting risperidone injection in the Fleischhacker et al. study (13). The sample included individuals who had been stable on their previous antipsychotic medication for at least four weeks before study entry and who were outpatients or who were inpatients and subsequently discharged. The overall hospitalization rate at one year was 17.6%; the rehospitalization rate for those beginning as outpatients and treated with risperi-done was 15.9%. This rate is notably lower than that reported for people receiving conventional long-acting agents (30-50%) or oral atypical antipsychotic agents (20-30%) (43,38,31,10). There was also a significant decrease in the percentage of patients requiring hospitalization (38% at baseline, 12% at the end of the study) (p < 0.0001) (6). Given the proportion of treatment costs due to hospitalization, use of long-acting risperidone injection could lead to an over-all reduction in the cost of treating schizophrenia.

Dosage and administration

On the basis of data from the studies by Kane et al. (22) and Fleischhacker et al. (13), the recommended starting dosage of long-acting risperidone is 25 mg administered every two weeks by deep intramuscular injection in the upper-outer gluteal area. Kane and colleagues (22) found that this dosage produced the optimum risk-benefit profile for most individuals with schizophrenia.
Given the lack of incremental benefits and the higher rate of EPSs seen with the 75-mg dose (22,13), the manufacturer recommends a maximum dosage of 50 mg every two weeks (17). Since the achievement of appreciable blood levels is delayed, supplementation with an antipsychotic should occur during the first three weeks after the initial injection. Because there is minimal release of risperidone from the long-acting formulation in the first three weeks, adverse effects arising from the presence of both oral and injectable medication are unlikely.

Steady state is reached after four injections of long-acting risperidone are administered every two weeks (six weeks of treatment). If breakthrough psychotic symptoms occur before steady state is reached, clinicians should treat them with an oral antipsychotic, rather than with increasing doses of long-acting risperidone. Clinicians should avoid giving rapidly escalating doses or extra injections in an effort to produce a quick response, since the effects of the dosage adjustments will not be evident for several weeks. Dosage adjustments should not be made more frequently than once every four weeks.

Patients with schizophrenia who are switched from an oral antipsychotic to long-acting risperidone injection should continue to receive their oral antipsychotic medication for the first three weeks of long-acting risperidone treatment. The duration of action of depot conventional antipsychotics is such that most patients who are switched from these agents can be directly switched to long-acting risperidone, substituting the long-acting risperidone for their next scheduled injection (30). Once steady state has been achieved, any missed doses should be administered as soon as possible. If the last dose was administered less than six weeks earlier, oral supplementation may not be necessary. However, if more than six weeks has elapsed since the last dose, oral supplementation should be considered. If doses are missed before the achievement of steady state, the clinician should provide oral supplementation when reinitiating therapy with the long-acting formulation. All patients should be carefully monitored (41).

Before patients are given long-acting risperidone injection for the first time, it is good clinical practice to rule out potential hypersensitivity. Clinicians can give a test dose of oral risperidone to evaluate hypersensitivity (21). Finally, since long-acting risperidone is injected in the form of a suspension, it should never be administered intravenously.

Conclusion

Long-acting injectable antipsychotic agents can limit the impact of partial compliance by helping to ensure delivery of antipsychotic medication. Depot conventional antipsychotics are usually reserved for people with disorders that are severe or difficult to manage. With its unique tolerability and efficacy, long-acting risperidone injection has the potential to extend the benefits of assured medication delivery and improved long-term outcomes to more patients with schizophrenia.
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NEUROBIOLOGICAL ARGUMENTS FOR A DEGENERATIVE MODEL IN SCHIZOPHRENIA

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Abstract
The cognitive dysfunction and structural alterations in the cortical and subcortical areas of the brain, as well as schizophrenia-like symptoms that appear in the course of neurodegenerative disorders, such as Alzheimer’s, Parkinson or Huntington diseases raise the question of possible etiopathogenic relationships between schizophrenia and neurodegenerative diseases. Based on different types of vulnerability, we try to elaborate a comparison between the two categories of disorders, leading to a model that could facilitate the development of primary and secondary prophylactic strategies and a individualized, neuroprotective therapeutic approach, based on the neurobiological submodel.

Keywords: schizophrenia, neurodegenerative disorders.

Several arguments that involve symptoms of schizophrenia such as cognitive dysfunction, progressive structural alterations of the cortical and subcortical areas, “schizophrenia-like” psychotic features in neurodegenerative disorders – dementia in Alzheimer’s, Parkinson or Huntington diseases bring once more into discussion the neurodegenerative elements in schizophrenia.

The involvement of neurodegenerative elements is sustained by at least two different sources of cerebral vulnerability, thus suggesting separate neurobiological models. The first source does not show structural alterations and is correlated with a short prodromal symptomatology without cognitive dysfunction, while during the active phase the positive symptoms are prominent (non-microlesional source). The other source associates frequently neurostructural changes, especially in thalamic, hippocampal and prefrontal areas, which are significantly correlated with toxic and traumatic aggressions during the intra-, peri- and postnatal periods (neurodevelopment abnormalities). The prodromal phase is long (more than 5 years) and the active phase is dominated by the cognitive, negative and depressive symptoms (microlesional source).

The structural microlesions represent the first trigger of the neurodegenerative potential, being similar to the notions of “minimal brain dysfunction” or “minimal brain damage”. Their impact in the

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etiology/pathogenesis of schizophrenia has raised proportionally with the neurobiological investigation techniques and was associated with birth trauma and metabolic or hypoxic alterations in the perinatal period. They constitute the first neurobiological model – the microlesional model (Figure 1).

Fig. 1. Cerebral abnormalities in first episode of schizophrenia. (adapted after Okubo, 2001)

Frequent neurological “soft signs” were identified for this model. Their existence, combined with minimal prodromal symptoms, represents a high risk for schizophrenia in child and adolescent (Erlenmeyer-Kimling & Cornblatt, 1987, Leask, Done & Crow, 2002). Adding to these cases structural abnormalities of the anterior cingulate cortex may transform into an ”ultra high risk” factor for the development of psychotic symptoms (Yucel, 2003).

Longitudinal studies regarding the evolution of patients with schizophrenia have shown that structural abnormalities progress together with the cognitive decline and the amplification of negative symptoms even in the absence of microlesional sources. This is a characteristic of schizophrenia that sustains the neurodegenerative model (Figure 2).

The progression of schizophrenia depends on the level of neuroprotection and intersynaptic connectivity, both between dopaminergic neurons and between their junctions with other neurotransmission systems. Protecting the functional structures represents an important objective in elaborating the therapeutic strategy.

The appearance of the disconne[ctive model may be primary – correlated with the microlesional vulnerability source – or secondary – through neurobiochemical alterations of regulation following disturbances in neurotransmission. Since there is a genetic predisposition similar to the neurodevelopment abnormalities, the early onset may constitute an indicator of the genetic
disconnective vulnerability and could also explain the rapid progression of neuronal loss (Figure 3). This may bring another argument in favor of the neurodegenerative model in schizophrenia.

**Fig. 2.** Comparison of ventricular enlargement volume changes for 10 years between a patient with schizophrenia and a control (adapted after Okubo, 2001).

**Fig. 3.** Average rates of grey matter loss in normal adolescents and in schizophrenia (adapted after Thompson, 2001)

The neurodegenerative elements in the Alzheimer’s disease determine an almost similar progression compared with the control (Figure 4).
The neurobiochemical vulnerability is potentiated by the genetic vulnerability that is correlated with the decrease in the capacity of neurotransmitters synthesis in the presynaptic pole. This dysfunction is revealed by presynaptic genetic markers (COMT, DBH and MAO). The pre- and post-synaptic vulnerability for dopamine triggers glutamate activatory mechanisms, which determine glutamatergic hyperactivity that is a crossing point between schizophrenia and neurodegenerative disorders.

**Increased Glutamatergic Neurotransmission in Schizophrenia**

- **Excitotoxicity - Firing of Dopaminergic Neurons in the Striatum and Mesocortical Structures:**
  - Relapse and positive symptoms;
  - Excessive NMDA Receptors activity;
  - Apoptotic risk / Decrease of neuroprotection.

**Fig. 5.** Neurobiological consequences of increased glutamatergic neurotransmission in schizophrenia

The primary deficit in dopamine is corrected by an exaggerated activity of glutamate, which first becomes excito-toxic with multiple secondary activations in the different neurotransmission systems. Thus, the initial hypodopaminergia is replaced with a hyperdopaminergic-like activity with polymorphic psychotic symptoms with neurotoxic risk. The increased glutamatergic activity reduces the GABA protection in the neuronal membranes, raising the excitability, altering the intra- and extracellular balance, the mitochondrial activity and the oxidative mechanisms. The result is the
appearance of the oxidative stress and the triggering of apoptotic mechanisms, common both for schizophrenia and neurodegenerative disorders. For both types of disorders, the clinical consequences may be frequent psychotic manifestations, while the neurobiological effect is the progression of atrophy in the white and grey matter.

**Fig. 6.** Progressive reduction of grey matter in schizophrenia is proportional with the duration of disorder and the number of relapses (after Kahn, 2006)

The reduction in dopamine activity following antipsychotic medication may be determined by the intense blockade of D2 receptors, generating extrapyramidal effects that are markers of disconnectivity and neurodegenerescence in schizophrenia.

Moreover, beside the hipodopaminergy a hiperglutamatery, the decrease in the cholinergic activity and the cholinergic blockade appear to be a common model for schizophrenia and Alzheimer’s disease, based on the following arguments:

- The behavioural, non-cognitive or hallucinatory symptoms in the history of Alzheimer’s disease could be controlled with cholinergic-like medication of glutamate modulators.
- Dopamine is proven to play an important role in the cognitive process
- Hipodopaminergy is correlated with the extrapyramidal induced symptoms

As a conclusion, the acceptance of a neurodegenerative model in the etiopathogeny of schizophrenia would facilitate the development of primary and secondary prophylactic strategies and an individualized, neuroprotective therapeutic approach, based on the neurobiological submodel.
References


THE CAMBRIDGE COGNITIVE EXAMINATION (CAMCOG) IN EARLY ASSESSMENT OF POST-STROKE COGNITIVE IMPAIRMENT

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Abstract
Stroke is one of the most common causes of cognitive impairment and dementia. The cognitive assessment of patients with stroke is very important in the early evaluation of the cognitive decline, thus preventing the severe dementia. The objective of our study is to assess the cognitive state in a group of 76 patients with ischemic stroke using the Cambridge Cognitive Examination (CAMCOG). We have also investigated the most affected cognitive domains. The patients in the group were between 72 and 84 years old, with an average educational level of 9 years and no aphasia. For comparison, a control group of 90 subjects was used, having the same range of educational level and age. Three assessments were done: at the beginning of the study, after 3 months and after 6 months. For the statistical analysis, the Student test (p<0,05) was used. The CT scan examination was performed in all patients. The patients with ischemic stroke have shown higher cognitive impairment than the control group and the cognitive decline increased after 6 months compared to baseline. Also, patients with ischemic stroke in left carotid territory have shown a higher cognitive decline compared with patients with ischemic stroke in right carotid territory or vertebro-basilar territory. The most affected cognitive domains were the memory, the praxis and the orientation.

Key words: cognitive decline, ischemic stroke, CAMCOG.

Introduction

Stroke is one of the most common causes of cognitive impairment and dementia. The cognitive decline installed after stroke is named "vascular cognitive impairment". It appears due to a complex interaction between vascular factors, the risk factors of stroke and neuronal damage of the brain. The cognitive assessment of patients with stroke is very important in the early evaluation of the cognitive decline, thus preventing the severe dementia.
Objective

The main aim of our study was to follow-up the cognitive performances of the patients who suffered an ischemic stroke, using CAMCOG. This scale assesses a wide area of cognitive domains, therefore we study which cognitive functions are the most impaired.

Material and methods

We studied a group composed of 76 patients aged between 72 and 84 years, and the mean level of education of 9,3±2,12 years. The patients were admitted to The Clinic of Neurology Craiova during 2007 year, for first ever ischemic stroke. We also studied a group composed of 90 control subjects without clinical signs of cerebro-vascular disease, with the same age and the same range of the educational level. 35 patients had an ischemic stroke in the left carotid artery territory, 30 in the right carotid artery territory and 11 of the patients in the vertebro-basilar territory. The diagnosis was confirmed by the CT scan examination. In all control subjects the brain computed tomography scans were normal. Data on conventional vascular risk factors were recorded for all the study subjects including arterial hypertension, diabetes mellitus, atrial fibrillation, dyslipidemia and smoking. Upon giving an informative consent, both groups (patients and controls) were tested using CAMCOG. It forms a part of a standardized psychiatric assessment schedule, CAMDEX (Cambridge Examination for Mental Disorders of the Elderly), devised by Roth and colleagues and published by Cambridge University Press. CAMCOG assess a wide range of cognitive domains such as attention, memory, abstraction, language, praxis, orientation and perception. The maximum overall score is 105. A cut-off of 80 was found to discriminate between demented and normal subjects. Our evaluations were made in the beginning of the study (baseline), then 3 months and respectively 6 months later. We compared the results obtained in the patients group with those from control group and we have also followed-up which are the most impaired cognitive functions assessed by CAMCOG. Then, we estimated the cognitive performances related to the vascular territory of stroke. The results were analyzed by Student test (p<0,05).

Results

At baseline, mean CAMCOG score in the patient group was 92,5 points and for the control group 94,2 points. After 3 months, the patients stroke showed a mean CAMCOG score of 88,4 points and the control group 92,2 points. Six months later, in the patients group we obtained a mean score of 83,5 points and in control group 90,1 points. The cognitive assessment related to the vascular territory showed the next mean CAMCOG values: the patients with ischemic stroke in the left carotid artery territory had at baseline a mean score of 90,1, after 3 months 86,8 points and at the end of the study 81,1 points. The patients with ischemic stroke in the right carotid artery territory had at baseline 92,8 points, after 3 months 90,8 points and 6 months later 88,7 points. In
the group of patients with stroke in the vertebro-basilar territory we obtained the next mean scores: at baseline 94,6 points, after 3 months 92,5 points and after 6 months 90,7 points. The statistical analysis regarding the most affected cognitive domains is represented on Table I.

Table I. The cognitive domains impaired in the patients and control group, using CAMCOG evaluation

<table>
<thead>
<tr>
<th>Cognitive domain impaired</th>
<th>Patients group (N=76) n%</th>
<th>Control group (N=90) n%</th>
</tr>
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<tbody>
<tr>
<td>Abstract thinking</td>
<td>41 (53,94%)</td>
<td>31 (34,44%)</td>
</tr>
<tr>
<td>Orientation</td>
<td>61 (80,26%)</td>
<td>70 (77,77%)</td>
</tr>
<tr>
<td>Language</td>
<td>37 (48,68 %)</td>
<td>49 (54,44%)</td>
</tr>
<tr>
<td>Memory</td>
<td>68 (89,47%)</td>
<td>79 (87,77%)</td>
</tr>
<tr>
<td>Attention and calculation</td>
<td>37 (48,68 %)</td>
<td>42 (46,66%)</td>
</tr>
<tr>
<td>Praxis</td>
<td>57 (75%)</td>
<td>68 (75,55%)</td>
</tr>
<tr>
<td>Perception</td>
<td>33 (43,42%)</td>
<td>28 (31,11%)</td>
</tr>
</tbody>
</table>

Conclusion and discussions

Given the increased number of elderly population, dementia of any type represents a common illness today, and efforts are made to enable early diagnosis and treatment as soon as possible. The studies of neuro-epidemiology suggested that the vascular factor is very important for starting and progression of dementia. As vascular pathology appears to be a common characteristic of both vascular dementia and Alzheimer disease, the early diagnosis of mild cognitive impairment must play an important role. This is one of the reasons to study the vascular cognitive decline.

Using CAMCOG for the cognitive assessment, we observed that the stroke patients group showed a higher cognitive decline than control group, both after 3 and 6 months (Fig. no. 1).

Our study in dynamics show that in the patients group there are not considerable statistically differences between cognitive state at baseline and 3 months later. After 6 months of
study we observed a considerable cognitive impairment in the patients group (p < 0.05), therefore our conclusion is that a considerable cognitive decline appears in the evolution of the patients with ischemic stroke. Regarding the relationship between the vascular artery territory and the range of the cognitive decline, our data shows a higher cognitive impairment in patients with ischemic stroke in the left carotid territory than in those patients with ischemic stroke in the right carotid territory and vertebrobasilar territory (Fig. no. 2).

As CAMCOG assess a wide area of cognitive domains, it gives the opportunity to observe which cognitive functions are the most affected in patients with ischemic stroke compared with those in the control group during the 6 months of study. The results pointed to the orientation, praxis and memory (Fig. no. 3 and 4).
Fig. no. 4. The impaired cognitive domains in control group

Our results are in concordance with other studies that demonstrated CAMCOG as a very useful tool in the assessment of cognitive decline. Using CAMCOG scale may offer an early detection of the cognitive impairment, thus preventing or slowing the progression to severe dementia.

References
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