SUICIDE BEHAVIOUR OF PATIENTS TREATED WITH ANTIDEPRESSANTS

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ANTIDEPRESSZÍVUMMAL KEZELT BETEGEK ÖNGYILKOS MAGATARTÁSA

Annak ellenére, hogy az antidepresszívumok meggyőzően hatásosak depresszióban és csökkentik az öngyilkosság veszélyét, van rá adat, hogy ronthatják a betegséget és igen ritkán az öngyilkossági hajlamot. Néhány irodalmi esetleírás érzékeltette, hogy különösen az SSRI antidepresszívumok ronthatják az öngyilkossági veszélyt, különösen a gyógyszerelés kezdetekor, akathiziában, nyugtalanság és agitáció esetén. A szuicid magatartás provokációja az antidepresszívumok súlyos mellékhatása lehet. Antidepresszívum adásakor az öngyilkossági hajlam kétszer gyakoribb, placebóval történt összehasonlításnál; ugyanakkor nagy a kontraszt, ha azt vizsgáljuk, hogy a kezeletlen depresszióban kétszer-hatszor nagyobb az öngyilkosság veszélye, mint a kezdetben. Az antidepresszívum és az atípusos antipszichotikum kombinációja hatásos lehet.

KULCSSZAVAK: depresszió, öngyilkossági veszély, antidepresszívumok, mellékhatás

SUMMARY

Although antidepressants undoubtedly treat depression and decrease suicidality in case of severely ill depressives in the case of good clinical response, there is evidence that antidepressants can worsen depression and can increase suicidality in a very small subpopulation. Some individual case histories were published that of SSRIs can induce suicidal behaviour, mainly at the beginning of the treatment, during akathisia, restlessness and agitation. Some clinical trials suggested that provocation of suicidality could be a serious side-effect of antidepressants. The almost double frequency of suicidal behaviour of patients on antidepressants compared to patients on placebo; it is in sharp contrast with the 2-6 fold lower suicide risk of antidepressant treatment versus untreated patients.

KEYWORDS: depression, suicide risk, antidepressants, side-effect

Since most patients suffering from major mood disorders attempt and commit suicide most frequently during major depression, (Rouillon et al., 1991; Isometsa et al., 1994; Tondo et al., 1998) untreated major mood disorders are a crucial risk factor for this very complex and multicausal human behaviour (Rihmer et al., 2002; Baldessarini et al., 2003). Several large-scale, naturalistic, observational, long-term follow-up studies (including severely ill, frequently suicidal unipolar and bipolar depressives) demonstrated that compared to no treatment, the risk of completed suicide of patients on long-term pharmacotherapy (antidepressants and/or mood stabilizers) is 2-6 fold lower (Leon et al., 1999; Angst et al., 2002, Baldessarini et al., 2003, Yerevanian et al., 2003; 2004). This emphasises the importance of treating acute mood episodes effectively and stabilizing the period of euthymia in suicide prevention.

In the last two decades we witnessed a 6-8 fold expansion of the prescription of antidepressants (mainly SSRIs) in several European countries where the suicide mortality has been traditionally high (Denmark, Hungary, Germany, Austria, Estonia, Switzerland, Sweden, Finland). This rise has been paralleled by a 54-26% decline of the suicide rates in these countries (Isacsson, 2000; Rihmer, 2001; 2004). These results support that if the rate of effectively treated depressions in the population increases, it results in the decrease of suicide rates.

In countries with low suicide rates (Australia, Northern Ireland, Iceland and Italy), however, the approximately 5-fold or less increase in the

selling of antidepressants has not resulted in a substantial decrease of suicide rates (Barbui et al., 1999, Hall et al., 2003; Kelly et al., 2003; Helgason et al., 2004), although studies from Australia (Hall et al. 2003) and from Northern Ireland (Kelly et al., 2003) described a significant association between increased antidepressant prescribing and fall of suicide rates in the different age cohorts over 30 years of age. In Italy, on the other hand, the national suicide rate did not change substantially between 1988 and 1994, and during this period the sales of antidepressants increased "only" by 36% (Barbui et al., 1999), a growth rate which is much smaller than the 5-8 fold increase in other countries, mentioned above.

The results of several studies support that increasing antidepressant prescription by itself explains decreasing suicide rates. In the United States between 1985 and 1999 the fourfold increase in antidepressant prescription was significantly correlated with a 13.5% decline of national suicide rate, with changing rates of unemployment and alcohol consumption having no effect (Grunebaum et al., 2004). A significant correlation between the increase of SSRI prescription and decreasing national suicide rates has also been found in another study after controlling for socio-demographic (unemployment, gender distribution, GDP, divorce rate etc.,) factors in a study investigating the antidepressant sale data and suicide rates of 27 countries (Ludwig and Marcotte, 2005).

Although antidepressants undoubtedly treat depression and decrease suicidality in case of severely ill depressives in the case of good clinical response, there is, however, evidence that antidepressants can worsen depression and can increase or even induce suicidality in a very small, vulnerable sub-population (Benazzi, 2003a, Healy, 2003). In the early 1990's, several controlled, individual case histories of "SSRI-induced suicidal behaviour" were published suggesting that antidepressants (particularly SSRIs) may induce suicidal behaviour mainly at the beginning of the treatment, a phenomenon which most authors related to the generation of akathisia, restlessness or agitation (Healy, 2003). Several meta-analyses of phase 2-3 randomized, controlled antidepressant trials (RCTs) also supported this possibility (Kahn et al., 2000; 2001; 2003; Culpepper et al., 2004; Whittington et al., 2004), and consequently various national authorities, including the British Medicines and Healthcare Products Regulatory Agency (MHRA) and the U.S. Food and Drug Administration (FDA) claimed that provocation of suicidality could be a serious side-effect of SSRIs and other antidepressants, primarily in a paediatric population.

These studies, however, cannot be considered representative for suicidal depressives, because severely ill, actively suicidal depressives, and patients with bipolar I and bipolar II depression are excluded from the RCTs. Nevertheless, RCTs could provide some useful, albeit limited information on this topic. The meta-analysis of committed suicides in phase 2-3 RCTs found that the annual rates of committed suicide were 0,6-0,9% with antidepressants and 0,3-0,5% with placebo (Kahn et al,, 2000; 2001; 2003). Comparing the SSRIs, other antidepressants and placebo in the FDA summary reports of phase 2-3 RCTs including 48.277 depressed patients, the results showed that the annual incidence of committed suicides of patients on SSRIs, on other antidepressants and on placebo were 0,58%, 0,76%, and 0,45%, respectively (Kahn et al., 2003). Furthermore, the meta-analysis of the 25 paediatric antidepressant drug-trials including more than 4000 patients, showed that 3,2% of children on antidepressive therapy became "suicidal", compared to 1,7% of those taking placebo. It should be noted, that no patients in these drug-trials completed suicide (Culpepper et al., 2004; Whittington et al., 2004). Short-term RCTs in adults, on the other hand, also indicated that newly emerged suicidal ideation was relatively rare (3,6% for TCAs, 1,2% for fluoxetine and 2,6% for placebo), and that in 70-72% of cases, antidepressants (mainly SSRIs) markedly decreased suicidal tendencies (that were present in one third of the patients at baseline), while the same rate for placebo was "only" 55% (Beasley et al., 1991; Montgomery et al., 1995).

The almost double frequency of suicidal behaviour of patients on antidepressants compared to patients on placebo in RCTs is in sharp contrast with the 2-6 fold lower suicide risk of treated versus untreated patients, reported in clinical studies on severely ill, frequently suicidal depressives. Is it possible that antidepressants prevent suicide more frequently among severely depressed, suicidal patients, but provoke such behaviour in less severe, actually non-suicidal depressives? Patients are usually in an activated state at the time of becoming suicidal while on antidepressants. This state which has long been well-known ("increas-

ing activity and energy level before improvement of mood") and has recently been named as „Activation Syndrome", occuring mainly in the initial phase of the antidepressant-treatment (Culpepper et al., 2004). Several years ago, however, in some clinical reports the authors described a group of "overzealous" depressives treated with TCA, MAOI, who developed refractory agitated depression characterized by intra-depressive excitatory symptoms, including mood instability, panic attacks and suicidality. Most of these major depressive patients had bipolar family history and responded well to lithium or neuroleptic augmentation (Akiskal and Mallya, 1987; Koukopoulos et al., 1992; Haykal and Akiskal, 1999). This "overactivated" or "overzealous" clinical state, mentioned above, highly corresponds to the activation syndrome (Culpepper et al., 2004), and the majority of the symptoms of activation syndrome such as agitation, irritability, hostility, impulsivity (and by definition hypomania and mania) are also the typical symptoms of the depressive mixed state (i.e. 3 or more hypomanic symptoms during a major depressive episode, Akiskal and Benazzi 2003; Maj et al., 2003). Since agitated depression and depressive mixed state are almost identical conditions (i.e. agitation in major depressive episode is mainly the consequence of the intra-depressive hypomanic symptoms) (Akiskal, Benazzi 2003; Maj et al., 2003; Akiskal et al., 2005), and agitated depression/depressive mixed starte increases the risk of suicidal behaviour (Benazzi, 2003b, Busch et al., 2003; Maj et al., 2003; Akiskal et al., 2005), it is very likely that the antidepressant-suicidality connection is mediated by depressive mixed state (Akiskal et al., 2005; Akiskal and Benazzi, 2005, in press). Antidepressant monotherapy, unprotected by mood stabilizers/antipsychotics in bipolar and bipolar spectrum disorder (including agitated unipolar depressions) can induce not only hypomanic/manic switches and rapid cycling, but can also worsen the preexisting mixed state, and this way can increase the risk of aggressive/suicidal behaviour (Akiskal, Mallya 1987; Ghaemi et al., 2002; Benazzi, 2003a; Dunner, 2003; Akiskal, Benazzi, 2005, in press). Recent studies, showing that 80% of antidepressant-resistant "unipolar" depressives have threshold, but most commonly subthreshold bipolar disorder (Sharma et al., 2005), and results indicating that in case of antidepressant-treated depressives the rate of prior suicide attempts is three-times higher among unrecognized versus recognized bipolars (Shi et al., 2004) also support this theory. Since over 50% of bipolar II, and around one-third of unipolar depressives have depressive mixed state (Benazzi et al., 2002, Benazzi, 2003b, Akiskal and Benazzi, 2003), but the rate of depressed patients who become suicidal on antidepressants is much lower, a more specific clinical description of the characteristics of the vulnerable sub-population is required. The question whether the combination of antidepressants with mood stabilizers or with atypical antipsychotics could also reduce suicidality in these patients is also an open question and needs further clinical studies.

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