REVIEW ARTICLE

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Association between Leukotriene-Modifying Agents and Suicide

What is the Evidence?

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Abstract

The US FDA has issued safety alerts and required manufacturers of leukotriene-modifying agents (LTMAs), including montelukast, zafirlukast and zileuton, to include suicide and neuropsychiatric events as a precaution in the drug label. This paper reviews the existing evidence on the potential association between the LTMAs and suicidal behaviour. We conducted a literature search of MEDLINE, EMBASE and International Pharmaceutical

Abstracts from 1995 to 2010 (inclusive) to identify pertinent studies and reports. We also examined data obtained from the FDA adverse event reporting system. To date, there are no well conducted, comparative, observational studies of this association, and the safety alerts are based primarily on case reports. While the FDA safety alerts apply to all three LTMAs, montelukast (known by its trade name Singulair®) is by far the most widely used of these drugs and most of the reports to date regarding suicide pertain to montelukast. From 1998 to 2009 there were 838 suicide-related adverse events associated with leukotrienes reported to the FDA, of which all but five involved montelukast. Nearly all cases were reported in 2008 and 2009 (96.1%) after the FDA warnings. LTMAs are approved for use in asthma and allergic rhinitis, and are effective drugs. Both of these diseases are also associated with suicide, making confirmation of the association more difficult. Given the lack of good evidence, we recommend that a large observational cohort or case-control study be conducted to quantify the association between LTMAs and suicide. Until then, when prescribing LTMAs, clinicians should consider the potential for suicide and monitor patients who may be at elevated risk carefully for suicidal ideation or psychiatric symptoms associated with suicidal behaviour.

Suicide is a significant public health issue. In the US, there were 33 300 people who died from suicide in 2006, making it the 11th leading cause of death, while approximately 1 million people die worldwide from suicide each year.[1,2] The US and global age-adjusted rates of death from suicide are 10 and 16 per 100 000 population, respectively.[1,3]

Males are at a nearly 4-fold greater risk for completed suicide compared with females, with White males having the highest rate at 19.8 per 100 000 population.[1] Suicide occurs both in adolescents and adults, with rates increasing until middle age, declining around age 50–70 years, and then increasing again late in life (age >75 years), particularly in males (figure 1).[3]

While there are many reported risk factors, >90% of suicides in the US are associated with psychiatric illness.[4] The most common type of psychiatric illnesses that are associated with suicide are affective disorders, which are present in more than half of all suicides, followed by substance abuse and schizophrenia.[5] Studies have reported suicide in 4–15% of people with depression,[6] bipolar disorder[7] and schizophrenia.[8] Increased risk of suicide has also been reported among those with dementia,[9] eating disorders,[10,11] anxiety[12] and panic disorders, attention-deficit disorder,[13] personality disorders[14] and body dysmorphic disorder.[15,16] Besides psychiatric illness, a previous suicide attempt is the strongest

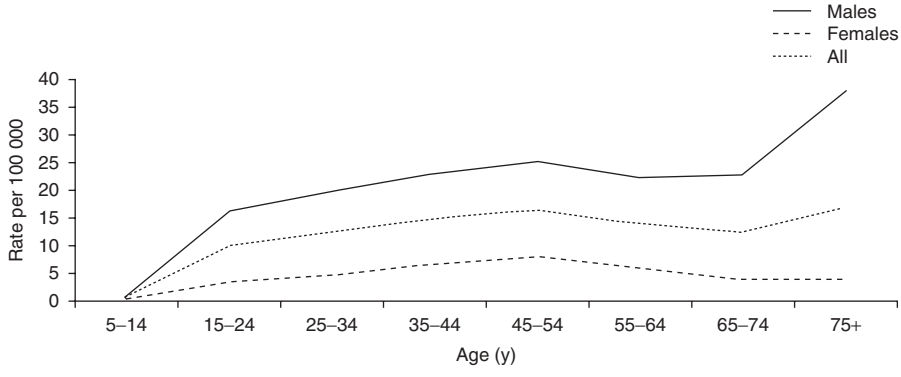

Fig. 1. Suicide rate (per 100 000 population) by age and sex in the US, based on data from the WHO.

Table I. Leukotriene-modifying agents available in the US

Generic name	Trade name	Manufacturer	US FDA-approved indication (date)
Montelukast	Singulair®	Merck & Co., Inc.	Asthma (20 February 1998) Allergic rhinitis (31 December 2002)
Zafirlukast	Accolate®	AstraZeneca Pharmaceuticals	Asthma (26 September 1996)
Zileuton	Zyflo® and Zyflo CR®	Cornerstone Therapeutics Inc.	Asthma (9 December 1996)

CR = controlled release.

predictor of repeated attempts, whether fatal or non-fatal.[17]

Over the past 5 years there has been an increasing recognition of the potential for certain prescription medications to increase the risk of suicide.[18] Based primarily on spontaneous adverse drug event reports (e.g. via the MedWatch system), the US FDA has issued warnings about psychiatric symptoms and suicidality for whole classes of medications, including selective serotonin receptor inhibitors,[19-22] which was expanded to all antidepressants,[19,23] antiepileptic drugs (AEDs)[24] and, more recently, leukotriene-modifying agents (LTMAs).[25-27]

The LTMAs, which in the US include montelukast, zafirlukast and zileutron, are effective drugs for the treatment of asthma and allergic rhinitis (table I). A fourth LTMA, pranlukast, is available in Latin America. Among these, montelukast is the most widely used. In 2009, Singulair®, the brand product of montelukast, was ranked number seven among the top selling prescription drugs in the US, with $US3.0 billion in sales,[28] while worldwide sales of Singulair® were $US3.6 billion (2006).[29] The widespread use of LTMAs heightens the concern about the potential association with suicide. At the same time, excessive caution could mean that effective therapies are withheld from patients who could benefit from them.

In this article, we review the evidence for the potential association between LTMAs and suicide, and we make recommendations for current practice and future research. We are aware of only one previous excellent review on this subject,[30] which we expand and update here.

1. Literature Search Strategy

A search of the literature databases MEDLINE, EMBASE and International Pharmaceutical Abstracts was conducted to identify studies and reports in the literature relevant to this review. This combination of databases has been determined optimal for literature of this type.[31] Primary search terms used were 'suicide', 'asthma', 'allergic rhinitis' and 'leukotriene-modifying agents', including the respective generic and trade names of each of the LTMAs marketed in the US, including 'montelukast', ('Singulair'), 'zafirlukast' ('Accolate'), and 'zileuton' ('Zyflo'). Because LTMAs were first approved for marketing in the US in 1996, we limited our search to articles published between 1995 and 2010 (inclusive). We also conducted internet searches using the Google search engine to find reports published online. The searches were filtered to exclude non-English articles.

To further inform this review, we examined empirical data obtained from the FDA Adverse Event Reporting System (AERS). These data were obtained by searching the FDAble database, a commercial source of FDA AERS data.[17] We restricted this analysis to reports of events where montelukast, zileuton or zafirlukast were the primary or secondary suspected drug associated with the event. Reports were identified where the terms 'suicide' or 'suicidal' were part of the Medical Dictionary for Regulatory Activities (MedDRA®) preferred term used by AERS for the reaction description. Where more than one suicide-related reaction was listed for a single case we used the higher order term in the following manner: completed suicide > suicide attempt > suicidal ideation > suicidal behaviour > depression suicidal. Only initial reports were counted and duplicate cases were eliminated. Data analyzed were from (inclusive) the first quarter of 1998 (earliest available) to the fourth quarter of 2009 (most recent available).

2. Suicide and Respiratory Diseases

Because LTMAs are used for both asthma and allergic rhinitis, it is important to recognize the underlying risk for suicide in these populations. Recent evidence establishes a probable link between common respiratory diseases and suicidal behaviour,[32] although the potential for such an association was initially identified as early as the mid-1960s.[33] Asthma and allergic rhinitis have each been linked to suicide, and these are also often co-morbid conditions, making the potential relationship to suicide even more complex.[34]

2.1 Asthma

Asthma is a chronic respiratory disease that affects about 38.4 million Americans during their lifetimes, and 300 million people worldwide.[35,36] Although asthma occurs in people of all ages, it is the most common chronic condition among children.[37] Adults with asthma are more likely to be female, whereas in children asthma more commonly affects males.[38]

People with asthma have been found to be at increased risk for a variety of mental disorders. Goodwin and colleagues[39] found that lifetime severe asthma was associated with the increased likelihood of anxiety disorder (odds ratio [OR] 2.09; 95% CI 1.3, 3.36), panic disorder (OR 2.61; CI 1.29, 5.25), panic attacks (OR 2.84; CI 1.66, 4.89), social phobia (OR 3.28; CI 1.42, 7.59), specific phobia (OR 2.93; CI 1.71, 5.0), generalized anxiety disorder (OR 5.51; CI 2.29, 13.22) and bipolar disorder (OR 5.64; CI 1.95, 16.35). Associations were even stronger in the time period during or immediately following an asthma exacerbation.

Asthma has also been associated with suicidal ideation, with ORs ranging from 1.9 in adults to 3.25 in youths (compared with those without asthma).[40-43] Asthma has been associated with a >4-fold (OR 4.34; $p < 0.001$) increase in the likelihood of a suicide attempt.[42,44] A recent study by Clarke and colleagues[45] suggests that people with asthma are more likely to have suicidal ideation and attempt suicide, than to have suicidal ideation without attempts. This would indicate that asthma is associated with suicide attempts rather than just suicidal ideation.

The reasons why those with asthma are more likely to commit suicide is unclear. A study by Harwood and colleagues[46] found that physical health problems were present in 82% of completed suicides in older adults. 'Breathlessness', along with pain and functional limitation, were the most frequent symptoms of health problems contributing to suicide in those with asthma. Concern about the symptoms of asthma may contribute to the various mental disorders (anxiety, panic, depression) that have been associated with the disease. Thus, it seems likely that depression or these other mental disorders are intermediate variables in the pathway between asthma and suicide.[47]

2.2 Allergic Rhinitis

Allergic rhinitis is a very common condition. Approximately 40 million people in the US, or approximately 10–30% of adults and 40% of children, have allergic rhinitis.[48] Similar prevalence is seen worldwide.[49,50] The disease typically presents in early school age and is characterized by sneezing, running nose and nasal congestion.[51] It is primarily caused by an allergic reaction to pollen or other allergens. Allergic rhinitis has traditionally been categorized as seasonal (now called 'intermittent') or perennial (now called 'persistent') based on the allergens being present either seasonally (or intermittently) or all the time (persistently). Seasonal allergic rhinitis is the more common type, although the prevalence of each is increasing worldwide because of increased exposure to allergens and airborne pollutants.[34] Allergic rhinitis results in 3.5 million lost workdays and 2 million lost school days annually, and has a negative impact on quality of life.[52,53]

The association between suicidality and allergies is not as clear cut as that with asthma. The link was first considered because of the observation that, contrary to what one might expect, suicides are more common in spring and summer than in fall or winter.[54,55] This observation was made in both hemispheres.[56-59] Of course, allergies too are more common in the spring. Subsequent studies

found seasonal variation in suicides rates in those with allergic disorders, with higher rates corresponding to peaks in disease.[60]

The reasons for the seasonal correlation between allergies and suicidality are not well understood, although a logical hypothesis is that spring-time increases in pollen result in the onset of symptoms of the disease, which leads to worsening mood or depression (the most common risk factor for suicide).[61] Allergic conditions have also been associated with other mental disturbances, including anxiety, depression, hostility/aggression and sleep disorders – all of which may also be related to suicide.[62-66] Thus, like asthma, it seems likely that depression or these other mental disorders may be intermediate variables in the pathway between allergic rhinitis and suicide.

Many asthmatics also have allergic rhinitis. Given the increased risk of suicide in those with allergic rhinitis, studies of the relationship between asthma and suicide clearly need to control for concomitant allergic rhinitis.

3. US FDA Alerts about Potential Association between Leukotriene-Modifying Agents (LTMAs) and Suicide

The FDA first issued a safety alert for Singulair® in March 2008.[67] In that communication, the FDA indicated that the manufacturer, Merck & Co., Inc., had ''updated the prescribing information and patient information for Singulair® to include the following post-marketing adverse events: tremor (March 2007), depression (April 2007), suicidality (suicidal thinking and behaviour) (October 2007) and anxiousness (February 2008)''. The FDA was apparently first alerted to the possible link between montelukast and suicide as a result of a media report of a 15-year-old in New York who killed himself 17 days after starting to take the drug for allergies.[68]

Subsequent to its initial communication (March 2008), the FDA requested the manufacturers of all three LTMAs, including montelukast, (Singulair®, Merck & Co., Inc.), zafirlukast (Accolate®, AstraZeneca) and zileuton (Zyflo® and Zyflo CR®, Cornerstone Therapeutics Inc.), to submit adverse event data for suicidality adverse events, as well as mood and behavioural-related adverse events, from all available placebo-controlled clinical trials. According to the FDA,[27] Merck & Co., Inc. reported one case of suicidal ideation but no completed suicides out of 9929 montelukast-treated patients across 41 placebo-controlled trials. There were no events among 7780 placebo patients. AstraZeneca reported no cases of suicidal ideation or completed suicide among 7540 zafirlukast-treated patients in 45 placebo-controlled clinical trials. However, there were two patients in the placebo group (out of 4659 = 0.04%) that had suicidality (one suicide attempt and one suicidal ideation). Cornerstone Therapeutics Inc. reported no cases of suicidal ideation or completed suicides in 1745 zileuton-treated or 1063 placebo-treated patients in 11 clinical trials. The FDA's conclusion from this analysis was that, while these data do not suggest that montelukast, zafirlukast or zileuton are associated with suicide or suicidal behaviour, these clinical trials were not designed specifically to examine neuropsychiatric events. A separate review of placebo-controlled paediatric studies of montelukast found similar results.[69] Among 2751 paediatric patients in four placebo-controlled multicentre studies, there were no neuropsychiatric adverse events.

In the same communication, the FDA provided information on postmarketing reports of neuropsychiatric events associated with the LTMAs. According to the FDA ''most of the reports of neuropsychiatric events are associated with montelukast, [but] the paucity of reports involving zafirlukast and zileuton make assessment of drug-induced effects with these limited''. Nevertheless, the FDA warned that ''patients and prescribers should monitor for the possibility of neuropsychiatric events associated with these agents''.[27]

The most recent communication from the FDA, dated June 2009, stated that postmarketing reports of patients on these medications included ''cases of neuropsychiatric events, [some of which] included clinical details consistent with a drug-induced effect''.[26] Finally, the FDA indicated that it had requested that manufacturers include a precaution in the drug prescribing information (drug labelling) for all three drugs.

4. Spontaneous Adverse Event Reports

A 15 January 2009 report from the Institute for Safe Medication Practices (ISMP, Horsham, PA, USA) provided a summary of adverse drug events related to montelukast that were reported to the FDA's MedWatch Safety Information and Adverse Event Reporting Program.[70] The report identified a surge in ''aggressive and suicidal behaviour in children and adults'' taking montelukast, with 644 cases identifying montelukast as the principal suspect drug in the second quarter of 2008 alone. The surge in cases was attributed to the FDA public alert in 2008, which presumably caused clinicians to become more aware of and report such events. According to the ISMP report, a total of 712 montelukast-related adverse event cases were received by the FDA in the 13 weeks after the initial FDA notice, whereas just 206 reports were filed in the 116 weeks prior to the notice. Among those cases listing 'psychiatric side effects', just 24 (4%) were received by the FDA prior to the initial safety notice, whereas 602 (96%) were received after the warning.

We reviewed suicide-related adverse drug events reported to the FDA AERS for all three LTMAs available on the US market for the period 1998–2009 (1998 being the earliest data available and 2009 the most recent). In total, we identified 838 LTMA-associated cases, with the majority (96.1%) occurring in 2008 or 2009. As shown in table II, suicidal ideation was the most common type of event, followed by suicide attempt and completed suicide. As shown in table III, montelukast was the suspected drug cause in all but five events (zileuton was the suspected cause in the other five, while there were no cases for zafirlukast). Among the 838 cases, an equal proportion were males (391 [46.7%]) versus females (384 [45.8%]), and the average age was 25.1 years (SD 19.6). Importantly, nearly all cases (96%) occurred in 2008 or 2009 (after the FDA warning).

Table II. Leukotriene-modifying agent suicide-related events reported to the US FDA by year and type of event[a]

Reaction	No. of events (% of total for major categories)			
	1998–2007	2008	2009	total
Completed suicide	4	67	32	103 (12.29)
Suicide attempt	10	108	30	148 (17.66)
Suicidal ideation	18	403	144	565 (67.42)
Suicidal behaviour	1	16	4	21 (2.51)
Depression suicidal	0	1	0	1 (0.12)
Total	**33 (3.9)**	**595 (71.0)**	**210 (25.1)**	**838 (100)**

a Includes events where reaction description included 'suicide' or 'suicidal' in term, and where montelukast, zileuton or zafirlukast was the primary or secondary suspected drug associated with the event.

Table III. Leukotriene-modifying agent suicide-related events reported to the US FDA (by year and drug)[a]

Drug	No. of events (% of total for major categories)			
	1998–2007	2008	2009	total
Montelukast	33	591	209	833 (99.4)
Zileuton	0	4	1	5 (0.6)
Zafirlukast	0	0	0	0 (0)
Total	**33 (3.9)**	**595 (71.0)**	**210 (25.1)**	**838 (100)**

a Includes events where reaction description included 'suicide' or 'suicidal' in term, and where montelukast, zileuton or zafirlukast was the primary or secondary suspected drug associated with the event.

Spontaneous reporting data such as these have a number of important limitations that have been reviewed elsewhere, not the least of which is lack of denominator data necessary to calculate a rate.[71] Clearly, other methods are necessary to further elucidate the causal association between LTMAs and suicide-related events.

5. Other Evidence of LTMA-Suicide Association

Besides spontaneous reporting data, the literature contains little other evidence to support the FDA precaution on LTMAs. After the initial FDA alert was issued, Holbrook and Harik-Kan[72] published an analysis of the association between montelukast and depression based on data from three previously published randomized controlled clinical trials involving 504 patients exposed to montelukast. Using emotional well-being as a marker for depression, they reported no evidence of a negative effect from montelukast. To the contrary, there was some evidence of short-time

improvement in quality-of-life measures of emotional well-being compared with placebo. They also reported no cases of psychiatric disturbances, suicide or depressive episodes in any of the patients who received montelukast in these trials. These data are of course limited by the small number of patients enrolled, indirect measure of depression used, exclusion of patients with previous psychiatric disorders and short-term follow-up.

The potential association between montelukast and neuropsychiatric events was first raised in 2001 when Biswas and colleagues[73] reported 36 cases of insomnia and 5 cases of depression among 15 612 patients treated with montelukast. Other adverse event case report-based data have been reported. A May 2007 report by the Netherlands Pharmacovigilance Centre (Lareb) summarized four cases of apparent montelukast-induced depression. Three of the four cases were in patients who did not suffer depressive symptoms prior to starting montelukast.[74] Depressive symptoms started soon after initiation of montelukast and ended with discontinuation of the drug.

In March 2008, Brunlof and colleagues,[75] using the Swedish adverse drug reaction (ADR) database (SWEDIS), reported a high number of safety events for montelukast used in children. Many of the adverse effects reported were neuropsychiatric in origin, including nightmares, sleep disorders, aggressiveness and anxiety. A follow-up study using the same database was published in June 2009 and used Bayesian Confidence Propagation Neural Network methods to confirm the signal.[76] In the follow-up, a total of 48 reports of psychiatric disorders in children during treatment with montelukast were identified. Psychiatric disorders reported more than once included nightmares, unspecified anxiety, aggressiveness, sleep disorders, insomnia, irritability, hallucination, hyperactivity and personality disorder; suicide was not reported. In most cases, time from exposure to ADR was <1 week. The authors reported that a positive statistical signal for psychiatric disorders was identified by the fourth quarter of 1998, and that the signal was even more significant by the fourth quarter of 2007. The authors concluded that psychiatric ADRs occurred during montelukast treatment in children more often than expected. Like other numerator-based analyses of spontaneous event reports, this study lacked consideration of the population at risk.

Only one retrospective cohort study on the association between montelukast and suicide has been published. Jick and colleagues[77] conducted a population-based cohort study using data from the UK General Practice Research Database. The investigators identified 23 500 patients exposed to one or more prescriptions for montelukast from February 1998 to March 2007, representing 21 050 person-years at risk. Only one case of suicide was identified, but this was in a woman who had been prescribed a single 28-day course of montelukast approximately 2 years prior to her death. The case was, therefore, ruled out and the author reported a suicide rate of zero. This study was limited by the relatively small sample size (especially given the low rate of suicide) and failure to include a comparison group.

6. Biological Plausibility of LTMA-Suicide Association

In addition to the limited evidence of an association between leukotrienes and suicidal behaviour, there is also no clear pharmacological mechanism through which montelukast or other leukotriene inhibitors might cause suicide or neuropsychiatric effects. Montelukast and zafirlukast are leukotriene antagonists, which bind and block the cysteinyl leukotriene receptor 1 ($CysLT_1$) in the cell membrane.[30] By blocking these receptors, the drugs prevent the effects of CysLTs (leukotriene C_4, leukotriene D_4 and leukotriene E_4), which act to recruit inflammatory cells, change vascular permeability, interfere with ciliary function and induce bronchoconstriction.[30] Zileuton works further upstream by inhibiting 5-lipoxygenase and thus the production of leukotriene A_4, which is eventually converted into the CysLTs.[78]

Leukotrienes do exist in the brain and CNS, but their exact role there is unclear.[79] As in other tissues, brain leukotrienes are involved in inflammation. Brain astrocytes and microglial cells generate several inflammatory mediators, including leukotrienes. These mediators and the components

of the complement cascade play an important role in the aetiology of most of the neuroinflammatory disorders.[80] It is also known that leukotrienes are involved in pain response.[79] At the same time, montelukast and other LMTAs penetrate the blood-brain barrier and can be found in significant concentrations in brain tissue.[81] In fact, montelukast has been studied as a neuroprotective agent in traumatic brain injury,[82] and for treatment of focal cerebral ischaemia[83] and migraine headaches.[84]

It has been suggested that inhibition of leukotriene receptors in the brain could be responsible for the neuropsychiatric adverse effects reported, although no causal mechanism has been proposed.[85] Another theory is that when montelukast binds to the $cysLT_1$ receptor it produces nitric oxides, which are toxic to brain tissue.[86] However, there appears to be no objective evidence to support this mechanism.

7. Recommendations

7.1 Recommendations for Research

There remains a lack of definitive data supporting the association between montelukast or other LTMAs and suicide.[87] As described above, the FDA stance is that ''the clinical details of some adverse event reports involving montelukast are consistent with a drug-induced effect'',[27] and has issued a precaution for the entire class. To the contrary, the American Academy of Allergy, Asthma and Immunology (AAAAI) and the American College of Allergy, Asthma & Immunology (ACAAI) have issued a joint statement stating that ''there are no data from well-designed studies to indicate a link between Singulair and suicide [and] it is unknown whether there is an increased incidence of suicide in patients receiving Singulair''.[87]

In our opinion, the AAAAI/ACAAI statement about lack of well designed studies is correct. As stated previously, the only cohort study conducted to date had an insufficient sample size and no control group for comparison.[77] Even considering the elevated baseline rate of suicide in those with asthma, the sample of exposed patients would likely need to be an order of magnitude larger to observe an effect from montelukast if one exists. In fact our preliminary estimates are that a sample in the tens of thousands would be necessary. Because of this, only a retrospective cohort analysis using existing data, such as a prescription and medical insurance-based claims or electronic medical record data, may be practical.

Such a study may have the added difficulty of the low level of occurrence of the outcome of interest. Completed suicide would presumably be the primary outcome of interest, although retrospective databases could include other relevant measures, such as suicide attempts, suicidal ideation and suicidal behaviour (generally considered an umbrella term).[88-90] While adverse drug event spontaneous reporting systems may include information on either suicide attempts or completed suicides, in medical claims data the most commonly available suicide-related outcome is suicide attempt. Suicide attempts are recorded in these data as event codes (e-codes) and likely suffer from underreporting. Linking information regarding exposure to LTMAs from prescription claims to data on cause of death (e.g. death from completed suicide identified in the National Death Index or other source) would be more reliable, but perhaps cost prohibitive.

7.2 Recommendations for Practice

Regardless of whether a true association exists between LTMAs and neuropsychiatric events, the presence of the FDA precaution and subsequent media attention has the potential to reduce utilization of these drugs in a manner similar to that which occurred in the case of antidepressants following their FDA warning.[91] The FDA warnings on antidepressants appears to have had a profound effect of reducing utilization of medications that are beneficial and necessary for people with serious disease.[92,93] It has been suggested that this resulted in a paradoxical effect of increased suicides, possibly because effective treatment was being withheld from patients who needed it.[94-96] In addition, good observational studies have now been conducted that show convincingly that the risk of suicide is lower, not higher, with exposure to the antidepressants.[91,97] The same may be

true for anticonvulsant medications, where recent data show that there may be no association between AEDs and suicide attempts.[98] The case of antidepressants and AEDs highlights the importance of weighing the benefits of early disclosure of potential but unconfirmed safety issues against the risks that may be incurred should those warnings result in the withholding of necessary treatment.

Given the current lack of evidence regarding the association between LTMAs and suicide, what are clinicians to do? Clearly one should not completely ignore the fact that such an association may exist. Nevertheless, given the effectiveness of LTMAs, these drugs should not be withheld in patients who might benefit from them. For now, taking extra precaution in those who may be at elevated risk for suicide and monitoring more carefully for neuropsychiatric effects is warranted.

8. Conclusions

While the FDA has issued alerts about the potential association between LMTAs and suicide, there are no well conducted, comparative, observational studies of this association. Until such studies are conducted (which we recommend) clinicians should consider this potential association when prescribing LMTAs, and should monitor patients who may be at elevated risk of suicide carefully.

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