

NEWS

Specific antipsychotic drugs prescribed for dementia could increase mortality

The largest US nursing home resident study reveals that different types of antipsychotic drugs have varying effects on the risk of mortality in elderly patients

Elderly patients treated with specific antipsychotic drugs for dementia are at increased risk of death, according to a population-based cohort study involving 75,445 nursing home residents aged 65 or older. The results emphasize the compelling need to develop alternative treatment methods for older patients with dementia.

Currently, up to a third of all elderly patients in nursing homes are treated with antipsychotic drugs. However, recently, concerns over the safety of antipsychotic drugs in the elderly have accumulated and, accordingly, the US FDA has issued advisory warnings for the use of both conventional and atypical antipsychotics in older patients. Researchers in the USA undertook the largest study involving US nursing home residents, to investigate the increased risk of mortality due to specific antipsychotic drugs: haloperidol, aripiprazole, olanzapine, quetiapine, risperidone and ziprasidone.

“The use of any antipsychotic in dementia is undesirable given the increased risk of death and the many other adverse effects of these drugs, in addition to their limited efficacy against target behavioral and psychological symptoms.”

It was found that there is variation in the risk of death according to the type of drug used. In comparison with risperidone, the reference group, haloperidol caused an increased risk and quetiapine caused a decreased risk of mortality within

180 days. The other drugs investigated did not demonstrate clinically meaningful differences. The effects of the antipsychotics were strongest soon after the initiation of treatment and remained after dose adjustment. There was a dose–response relationship for all drugs except quetiapine.

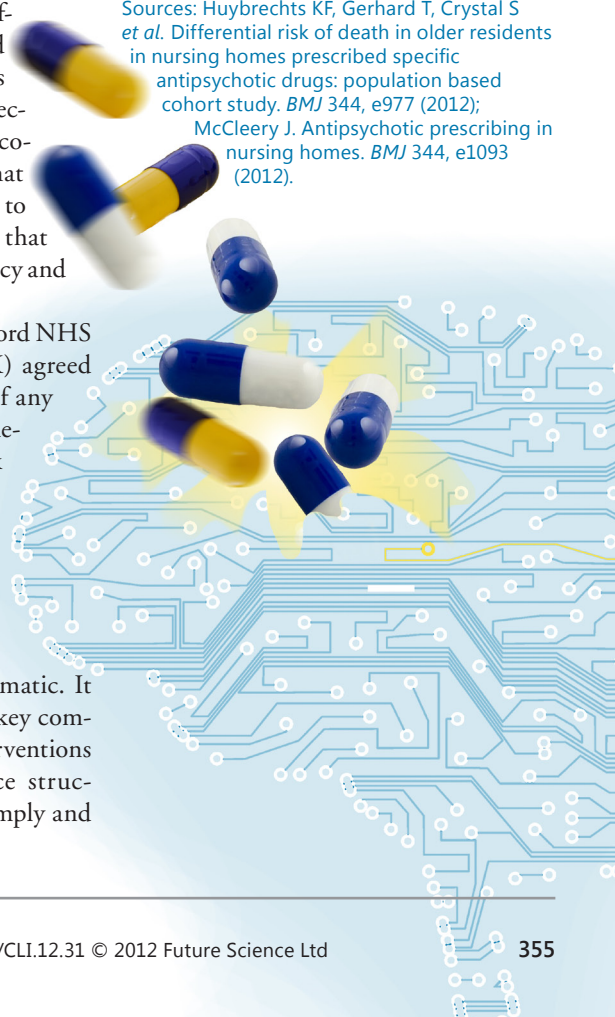
The authors of the study concluded that the “clinicians may want to consider this evidence when evaluating ... the best approach to treatment of behavioral problems.” However, they indicated that the current non-pharmacological interventions for dementia are often insufficient in patients with severe and persistent or recurrent symptoms and, in the absence of proven effective and safe alternative pharmacological treatments, it is likely that antipsychotic drugs will continue to be used widely, despite the fact that there is not evidence of their efficacy and data confirming their risk.

Jenny McCleery from the Oxford NHS Foundation Trust (Oxford, UK) agreed with this conclusion. “The use of any antipsychotic in dementia is undesirable given the increased risk of death and the many other adverse effects of these drugs, in addition to their limited efficacy against target behavioral and psychological symptoms.” She added that “future research should be pragmatic. It should focus on identifying the key components of non-drug-based interventions and on establishing the service structures that can deliver them as simply and efficiently as possible.”

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Written by Francesca Edelmann, Production Editor.

Sources: Huybrechts KF, Gerhard T, Crystal S *et al.* Differential risk of death in older residents in nursing homes prescribed specific antipsychotic drugs: population based cohort study. *BMJ* 344, e977 (2012); McCleery J. Antipsychotic prescribing in nursing homes. *BMJ* 344, e1093 (2012).



Improving clinical trials in molecular oncology

Oncologists have recently described a new outlook on patient participation in lung cancer trials with molecular preselection

In a recent paper in the *Journal of Thoracic Oncology*, Howard West from the Swedish Cancer Institute (WA, USA) and Ross Camdige of the University of Colorado School of Medicine (CO, USA) describe new suggestions for tackling the growing problem of patient recruitment in lung cancer trials for patients with specific mutations. They hope this research will influence new molecular oncology trial design and implementation.

Molecular preselection is becoming more prevalent in oncology clinical trials due to increased scientific knowledge on the basis of cancer progression. This means patients should be able to receive more personalized treatment. However, new issues have arisen in the implementation of these trials, since patients with specific mutations (required for a specific oncology trial) are more geographically dispersed.

“...geographic diversity of patients with these narrow clinical and molecular parameters will greatly limit the ability of trials to enroll patients from single centers.”

In the paper by West and Camdige various methods for tackling this problem are discussed, focusing particularly on lung cancer trials. First, the pair describe how online patient communities can assist in the advertisement of trials. West leads the Global Resource for Advancing Cancer Education (GRACE), which is an online social media community. In the paper he describes one particular success of this site – in February 2010, after publishing a podcast detailing one particular clinical trial, patients traveled from 15 different US states and one from South Africa to participate.

Leading on from this point, the authors identify that patients can additionally learn

much more about their condition through online educational resources. Speaking exclusively to *Clinical Investigation*, West explains a novel side to this increased patient knowledge base: “The dynamic of how physicians, at least oncologists, interact with motivated patients is shifting to a more bidirectional, collaborative mutual sharing of information, as opposed to a historically unidirectional approach of the physician having access to all of the medical management options and the patient relying on a single doctor to provide all insight and treatment recommendations.”

The authors also discuss how the structure of clinical trials needs to be updated to suit the new molecular basis of oncology research. As West explains, “geographic diversity of patients with these narrow clinical and molecular parameters will greatly limit the ability of trials to enroll patients from single centers.” He hopes that their work will encourage sponsors of clinical trials to invest in new strategies to fight this emerging problem. A key method described in their paper is telemedicine-based platforms, to enable remote selection and follow-up of patients enrolling in these trials. Telemedicine is defined as the use of electronic communication to exchange medical information between two sites. Additionally, the authors suggest that trial providers could reimburse either the patient or clinician for travel costs to remote trial sites, or host the trial at various disperse sites.

West details his plans for future work: “I am working on developing a telemedicine-based platform for consultations and general clinical oversight of patients who are a prohibitive distance away from an expert on their particular cancer. This approach could easily be applied to clinical research efforts as well, provided that forward-thinking research sponsors are inclined to overcome the bottleneck of low geographic density of their target research population.”

Written by Alice O'Hare, Assistant Commissioning Editor.

Source: West HJ, Camdige DR. Have mutation, will travel: utilizing online patient communities and new trial strategies to optimize clinical research in the era of molecularly diverse oncology. *J. Thorac. Oncol.* 7(3), 482–484 (2012).

Therapeutic misconception still prevalent in Phase I trials

The frequency of misconception amongst patients enrolled in Phase I clinical trials has been elucidated by a group of medical oncologists

In a research article, which is to be published in *Cancer*, Rebecca Pentz from the Emory University School of Medicine (GA, USA) and colleagues report their investigation into misconceptions held by patients enrolled in Phase I clinical trials. The research team's findings suggest more education is necessary to avoid the misconceptions still present in Phase I trial participants.

In their research two particular forms of misconception were studied. First, therapeutic misconception, which is when a patient believes the aim of the trial is to improve the health of the enrolled patients (i.e., a therapeutic aim), rather than to forward research. Second, therapeutic misestimation, which is when a patient wrongly understands the risks or chances of health benefits.

Although therapeutic misconception is a well-known issue to arise in clinical trials, the team felt there was a lack of recent “systematic, empirical evaluation” of the frequency of this, and other misunderstandings in clinical trial participants. The team interviewed 95 patients enrolled in Phase I trials. Of these patients, 68.4% of the interviewees were found to have therapeutic misconception. On further analysis this was found to be associated with lower education and family income, but not associated with a patient's lack of treatment options. A higher proportion of patients were found to have therapeutic misestimation, with 95% of patients falling into this category.

Additionally, the team investigated the patient's thoughts on the perceived risks and benefits of participating in the trial. They found that 39% patients mentioned the risks of investigational agents and 41% mentioned uncertain outcomes (due to this being research rather than tested therapeutics). Only 3% of patients mentioned the risks that could arise solely due to this being research, such as biopsies.

Looking to the perceived outcomes of the trial, the researchers found that slightly over half (54.6%) of the sample group were optimistic – defined by believing that “their chance of benefit was greater, and that their risk was lower than the population chance.”

Conversely only 37.6% were pessimists, believing the opposite.

The researchers conclude that therapeutic misconception is still high, and suggest that more education is necessary to avoid this lack of understanding.

Written by Alice O'Hare, Assistant Commissioning Editor.

Source: Pentz RD, White M, Harvey RD *et al.* Therapeutic misconception, misestimation, and optimism in participants enrolled in Phase 1 trials. *Cancer*. doi: 10.1002/cncr.27397 (2012) (Epub ahead of print).

US nationwide trial has implications for emergency seizure treatment

A national trial conducted across the USA comparing delivery of anticonvulsant medication may have implications for paramedics

Researchers from the University of Cincinnati (OH, USA) have collaborated with local paramedics to compare the efficacy and safety of two differing methods for delivering medication to seizing patients. Their research, to be published in the *New England Journal of Medicine*, has implications for prehospital care of seizing patients by paramedics.

Status epilepticus is defined as a prolonged seizure lasting more than 5 min. Traditionally, in this situation paramedics administer intravenous anticonvulsant medication. However, since this is relatively slow to administer, intramuscular administration (with an autoinjector, which is similar to an epipen) would be preferential to many in the medical profession. The aim of this clinical trial was to compare the efficacy of intramuscular midazolam with intravenous lorazepam for status epilepticus. The

researchers hypothesized that the intramuscular route would be found to be noninferior.

The research comprised part of RAMPART, and was carried out over a national scale – involving 79 hospitals and 33 emergency medical services agencies in the USA. The double-blinded, randomized trial was unusual in that the patients receiving the medication could not consent (due to their condition). Therefore, the trial was regulated under a special US FDA ruling “exception from informed consent,” and awareness of the trial was raised within the communities before the trial launch. Author Arthur Pancioli from the University of Cincinnati expressed gratitude to the public: “We would like to thank ... our community for their trust in allowing us to perform this study. Without this type of research, critical opportunities to help patients with neurological emergencies would be lost.”

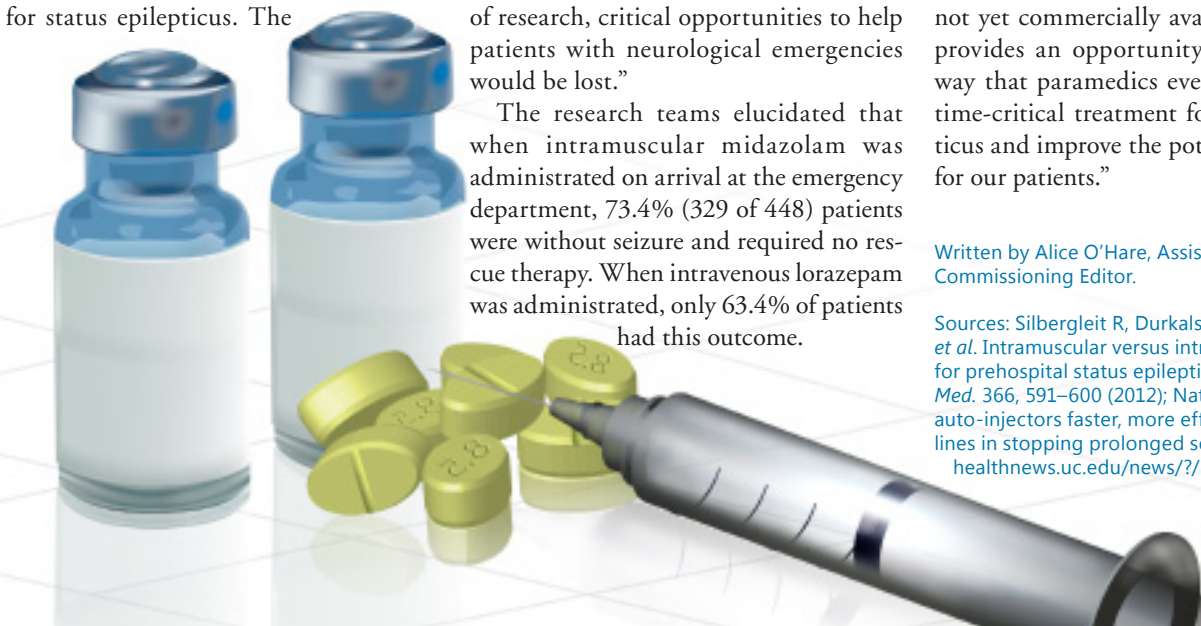
The research teams elucidated that when intramuscular midazolam was administered on arrival at the emergency department, 73.4% (329 of 448) patients were without seizure and required no rescue therapy. When intravenous lorazepam was administered, only 63.4% of patients had this outcome.

Looking at the scene of the emergency, intramuscular therapy was found to be administered within a median time of 1.2 min, compared with 4.8 min for intravenous administration. Conversely, the time it took for the medication to take effect (i.e., for the convulsions to stop) was a median of 3.3 min for intramuscular compared with 1.6 min for intravenous.

Overall, the research indicates that for status epilepticus, intramuscular midazolam is as safe and effective as the traditional intramuscular medication. Co-investigator Jason McMullan from the University of Cincinnati explains the implications of these results and future prospects: “The use of the auto-injectors could further improve the excellent care our paramedics provide to their patients every day. While the auto-injectors are not yet commercially available, this trial provides an opportunity to change the way that paramedics everywhere deliver time-critical treatment for status epilepticus and improve the potential outcomes for our patients.”

Written by Alice O'Hare, Assistant Commissioning Editor.

Sources: Silbergleit R, Durkalski V, Lowenstein D *et al.* Intramuscular versus intravenous therapy for prehospital status epilepticus. *N. Engl. J. Med.* 366, 591–600 (2012); National trial shows auto-injectors faster, more effective than iv lines in stopping prolonged seizures: www.healthnews.uc.edu/news/?/15315



Zioptan™ is approved by the US FDA

Zioptan™, an eye drop that aims to reduce heightened eye pressure, has recently been approved by the US FDA for use in patients with open-angle glaucoma or ocular hypertension

Ocular hypertension is a heightened pressure in the eye, which is a leading risk factor of glaucoma (the most common of which is open-angle glaucoma). This condition can in turn lead to blindness. Zioptan™, which is marketed by Merck (NJ, USA), is a prostaglandin analog. This type of medication works by increasing the removal of fluid from the eye.

Zioptan has been shown to be safe and effective in various long-term clinical trials. A total of 905 patients were enrolled over five clinical studies, the longest of which was 24 months. Patients treated with eye drop once daily in the evening

showed reduced eye pressure at 3- and 6-month intervals. The patients' eye pressures decreased from a baseline of 23–26 mmHg by an average of 6–8 mmHg at 3 months and 5–8 mmHg at 6 months.

“...Zioptan's approval provides an alternative treatment option for patients living with this potentially blinding disease.”

The director of the Office of Anti-microbial Products at the US FDA's Centre for Drug Evaluation and Research (MD,

USA), Edward Cox, explained the significance of this approval: “Zioptan's approval provides an alternative treatment option for patients living with this potentially blinding disease.” Merck expects their newly approved product to be commercially available in the near future.

Written by Alice O'Hare, Assistant Commissioning Editor.

Sources: FDA press release: www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm291966.htm; Merck press release: www.merck.com/newsroom/news-release-archive/prescription-medicine-news/2012_0213.html

Korlym™ approved by the US FDA for hyperglycemic control in patients with endogenous Cushing's syndrome

Korlym™, a therapeutic for the treatment of hyperglycemia in endogenous Cushing's syndrome, is the first of its kind to be approved by the US FDA

The US FDA has recently approved the use of Korlym™, a cortisol receptor blocker, for the control of blood sugar levels in certain adults with endogenous Cushing's syndrome. This subset of patients are characterized by Type 2 diabetes or glucose intolerance and fail to respond to, or are not candidates for, surgery. Endogenous Cushing's syndrome is defined by an overproduction of cortisol and thus this new therapeutic prevents the unwanted effects of this steroid hormone.

This is the first approved medicine for this condition, and accordingly the FDA

carried out specialized fast-track procedures to ensure the therapeutic reached the patients without undue delay. Among various studies, the safety and efficacy of Korlym has been proven in a clinical trial with 50 patients.

Korlym, which is marketed by Corcept Therapeutics (CA, USA), has been approved in a dosage strength of 300mg tablets. The company has approved the distribution of the drug through a central pharmacy, allowing better access for sufferers of this rare disease.

“...the FDA carried out specialized fast-track procedures to ensure the therapeutic reached the patients without undue delay.”

Written by Alice O'Hare, Assistant Commissioning Editor.

Sources: US FDA press release: www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm292462.htm; Corcept Therapeutics press release: www.corcept.com/news_events/pr_1329524335

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