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The management of agitation in demented patients with propranolol

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Abstract. Congress and the FDA have strongly suggested that tranquilizers and antipsychotics not be used in agitated demented frail elderly patients. The medical profession has not moved away from the tradition of antipsychotic sedation of such patients. Use of 'modern second generation low dose' antipsychotics continue to be the standard of care.
Propranolol, a non-selective β-blocker with good penetration of the CNS, is a reasonable and safe alternative to sedatives and antipsychotics. Anti-dementia drugs are complementary to propranolol. A case study which contrasts the two pharmacologic approaches is detailed. A method of estimating delirium-agitation risk in dementia patients (DRN method) is described.

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On April 12, 2005, the US Food and Drug Administration insisted on a Black Box warning label for second generation antipsychotics [1]. This warning included olanzapine, aripiprazole, risperidone and quetiapine. Analysis of 17 placebo-controlled studies showed a 4.5% mortality rate among elderly patients with dementia who had been treated for behavioral symptoms. The studies were, on average 10 weeks in duration and represented 5,106 patients with dementia.

This should not surprise physicians. In 1987, Congress discouraged use of sedatives in demented nursing home residents [2]. Adverse effects of second generation antipsychotics occur in frequencies exceeding 25%. These adverse events include cardiac arrest, extraprymidal syndromes, delirium, falls, hip fractures, hypotension, orthostasis, paralytic ileus, stroke, and truncal dystonia [3–6]. Nevertheless, years after Congress cautioned physicians, antipsychotics were the number one prescribed drug for Alzheimer's disease [7,8]. Professional articles on management of dementia behaviors continue to feature antipsychotics and sedatives [9–11]. At a cellular level, atypical antipsychotics result in long term changes in several neuroreceptors. Most important is downregulation of AMPA and NMDA receptors [12]. At a clinical level, recipients of antipsychotics can be expected to develop difficulties in memory which cannot be back-titrated with anti-dementia medications. Further, at a cellular level, antipsychotics are associated with neurotoxicity [13]. Some have actually suggested use of benzodiazepines as a drug holiday for antipsychotics [14].

In this context, propranolol would seem a reasonable alternative to sedatives and antipsychotics. Propranolol has been used to control anxiety and agitation for years [15,16]. But there is an unreasonable fear of propranolol. The author has heard arguments from colleagues that propranolol 1)aggravates cardiac conditions 2) causes falls and fractures 3) harms renal function or brain function and 4) is generally unsafe [17]. Paradoxically, these intuitive fears are erroneous.

In 1962, propranolol was the first clinical β-adrenergic receptor antagonist [18]. It remains unique in many ways from others in the class. It is the most lipid soluble of the β-blockers at 93.65 Log Kp and readily enters the CNS [19]. It blocks $\beta 1$ and $\beta 2$ receptors with equal affinity, and totally lacks intrinsic sympathomimetic activity. It has no α-adrenergic blockade effects. Propranolol is variably metabolized by the liver in the first passage via the portal vein. Only 10–45% reaches the systemic circulation. Thus, there

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are twenty-fold inter-individual variations in dose response. An effective dose in the elderly can range from 10 mg twice a day to 200 mg twice a day. Per the FDA Package Insert, the effective dose range varies from 20 mg to 640 mg per day. Dose finding begins at 40 mg bid. Relative contraindication are now limited to patients with bronchospastic diseases or known anaphylactic reaction. Caution is advised in substantial hepatic or renal failure.

Propranolol has a high therapeutic index. In 1997, Love et al. published the outcome of 22,948 propranolol overdoses [20]. There were only 27 fatalities. The rate of death per intentional overdose is about one per thousand events. In 1978, the Kroc Foundation held a conference on the use of high dose propranolol and schizophrenia [21]. Here doses up to 5,000 mg of propranolol per day were used. Curiously, a side effect of propranolol doses above 600 mg per day was a paradoxical rise (not drop) in blood pressure. Propranolol is remarkably safe.

The intuitive myth that propranolol causes heart injury, by slowing the heart rate and exerting negative inotropic effects, is wrong. Paradoxically, β-blockers are associated with clinically meaningful reduction in mortality and morbidity in patients with stable congestive heart failure [22]. Since 2001, β-blockers are a standard of care for stable congestive heart failure.

It is also a myth that falls and fractures are caused by propranolol. The presumed cause is propranolol induced hypotension. But, propranolol has been used to treat orthostatic hypotension due to autonomic dysfunction [23]. Further β-blockers significantly reduce the risk of fractures in elderly patients [24]. This study analyzed 30,601 patients up to age 79 over a ten year period. By way of contrast it is clear that use of tranquilizers and sedatives increase the risk of falling and fracture in elderly persons [6].

Propranolol prevents mitochondrial outer membrane permeabilization in vitro which leads to apoptosis [25]. Propranolol is suited to use in Alzheimer's cases, because it has neuroprotective properties. Propranolol would be synergistic with memantine.

1. Case study

LD is an ideal case to contrast the use of second generation neuroleptics versus propranolol. He was a 74 year old married male living in the open unit of a nursing home with minimal incident for one year. Prior to stabilization at the nursing home, he suffered late stage Alzheimer's disease complicated by disruptive vocalizations and episodic violent outbursts. At six foot four inches height he was quite intimidating. Agitation was controlled for over one year by removal of all antipsychotics. Concomitantly propranolol was titrated to a steady state dose of 60 mg po TID. This dose was arrived at by the titration schedule of Fig. 1. *LD* was also prescribed rivastigmine 3 mg bid, doxepin 25 mg HS, citalopram 40 mg per day, gabapentin 300 mg bid and aspirin 88 mg q day. Rofecoxib had been used intermittently for pain control of the right foot. Over the course of the year the patient had healed a stage three decubitus ulcer of the right foot complicated by methacillin resistant staphylococcal aureus infection. Acyclovir had been used for recurrent herpetic outbreaks. Diabetes was managed with diet alone. On rare occasions, chlorpromazine 12.5–25 mg was given IM for extreme paroxysmal agitation.

He was stable for a full year in the nursing home.

A first medical hospitalization occurred 119 days prior to death in hospital No1. The patient appeared septic due to profound fecal impaction. The marked increased intraabdominal pressure aggravated his renal condition. His BUN was 74 mg/dl and creatinine was 4.8 mg/dl. Nephrology consult felt the renal failure was multifactorial. Contributing were bowel obstruction, rofecoxib exposure, acyclovir exposure, right hydronephrosis of unknown etiology, and prostatic hyperplasia. Given the advanced dementia, it was elected to not aggressively evaluate *LD*'s renal disease. Repeated enemas decompressed the bowel, but this required repeated parenterally use of low dose chlorpromazine and occasional physical restraints. The neuroleptics resulted in increased confusion and agitation.

He returned to the nursing home, but was quite agitated. His BUN and creatinine has dropped to 50 mg/dl and 3.3 mg/dl respectively.

The first psychiatric admission occurred 105 days prior to death under the author's control in hospital No2. In seven days the patient's agitation was controlled by use of propranolol at 60 mg tid (180 mg/day). *LD* was sent to the nursing home, and the author went to a week long conference. The covering physician added olanzapine to control patient and he soon became unmanageable.

LD was sent to hospital No2 where his care was assumed by psychiatric hospitalists (Fig. 2, Plot A). He remained in at hospital No2 for 15 days, after an initial dosing with 12 mg haloperidol, 100 mg quetiapine, 25 mg chlorpromazine and 25 mg of olanzapine lozenges. The propranolol was rapidly tapered and re-

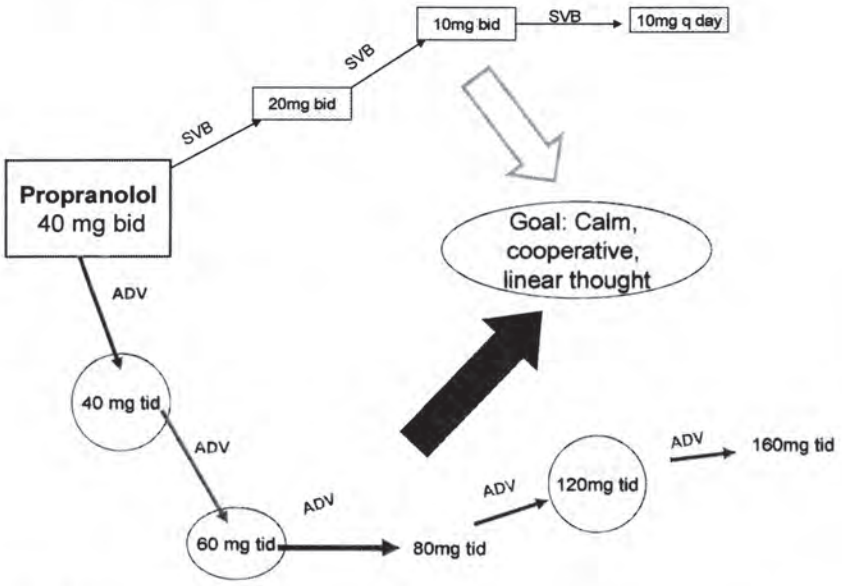

Fig. 1. SVB is sedated, Vasospastic, and breathing labored (wheezing) ADV means Agitation, Disruptive verbalization, or Violent

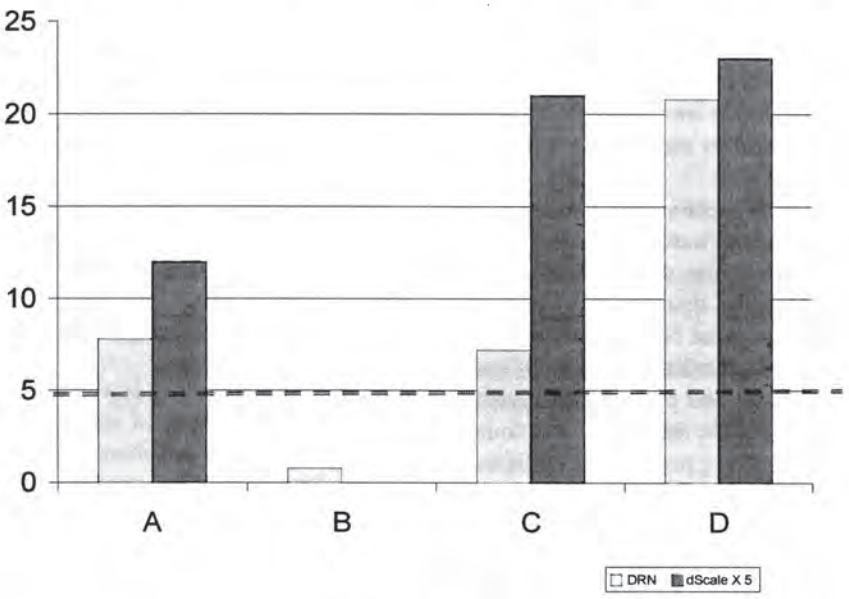

Fig. 2.

moved. The patient's daughter (and Power of Attorney) was convinced to change physicians. The "dangers" of propranolol were used to convince the daughter.

Seventy-seven days prior to death, the patient returned to nursing home on 100 mg/day dose of quetiapine. Within six days, he accelerated to incessant yelling and violence. He struck several staff members, a roommate and members of his family. He was sent to a medical hospital No1, where the author (both an internist and psychiatrist) re-assumed his care. Within seven days the patient's agitation was again controlled by elimination of tranquilizers and addition of propranolol 60 mg bid (120 mg/day). However, the nursing home refused to accept the patient back. Other placement with his history was a problem.

The author elected to move LD to hospital No2 until placement could be made (Fig. 2, Plot B). As a matter of courtesy, one of the hospitalists associated with

the earlier hospital No2 admission was asked to co-follow. This physician was hostile. He documented in the chart that propranolol was harming LD's heart, and discontinued it. Mentally the patient deteriorated rapidly. Cardiology consultation was obtained, and pointed out that beta blockade was now recommended for heart failure [22]. Per demand of this objecting hospitalist, the patient was scheduled for TURP thirty nine days prior to his death. The urologist was openly doubtful that this might be of value for the patient. This employee-physician then complained that propranolol was damaging the patient's kidneys. Nephrology consult was obtained. The nephrologist did not feel that the mild renal failure was caused by or aggravated by the propranolol. This physician then withdrew from the case in protest.

Thirty nine days prior to death, the patient was transferred to the surgical service of hospital No2 for a transurethral prostatectomy. The hospitalists of hospital No2 resumed their care of *LD*. Propranolol was removed and antipsychotics employed (Fig. 2, Plot C). Predictably, the patient became delirious.

On Christmas Eve the patient was returned to the nursing home, again under another physician's care. Within 36 hours he failed. He was refused admission by hospital No2. On return to the nursing home the patient did poorly.

Nineteen days prior to death, LD was sent to a hospital No3's psychiatric ward. Ziprasidone, lorazepam, risperidone, clonzapine, and quetiapine were employed. The record shows that hospital No3 staff contacted hospitalists at hospital No2 for advice. Accordingly they chose to use accelerating doses of quetiapine. He went from loud and periodically violent, to stuporous and not eating. On the day he was found dead in bed, *LD* was on 400 mg per day of quetiapine, and 900 mg per day of gabapentin and 1 mg of risperidone given prn over the prior 24 hours. He was not on any anticholinesterase drugs which are used to treat dementia. He was propranolol free.

2. Analysis

To assess the difference between the standard sedative approaches to control of dementia related agitation and the use of propranolol, two tools were used.

A modified Drug Risk Number (DRN) methodology gives a risk estimate of drug induced delirium [26]. The DRN method classifies each drug from I – IV as follows:

Class I – known synergistic effect with anticholinergic agents, but not known as a direct cause of delirium.
Class II – known to cause delirium, but currently not documented to have CNS anticholinergic properties.
Class III – known to cause delirium of anticholinergic type
Class IV – D2 antagonist antipsychotics used for ten or more days.
Class *negative* I – phosphatidylcholine
Class *negative*-III -anticholinesterases

At the time that the DRN number was devised, no cholinergic agonist medications were available for daily administration. When using a known anti-dementia drug, such as donepezil or rivastigmine, the number assigned is a negative Class III. These are strong cholinergic agonists. Phosphatidylcholine is a weak cholinergic agonist and classified as a negative Class I.

Special mention needs to be made of hypnotics and minor tranquilizers, such as lorazepam. These induce delirium by non-cholinergic influences but have been used in the past to pharmacologically establish presence of cholinergic driven dementias. As such they are Class III agents. D2 antagonist antipsychotics are special cases. These drugs include fluphenazine, haloperidol, perphenazine, olanzapine, quetiapine, ziprasidone, and risperidone. Such haloperidol like-drugs induce neuroreceptors changes over 7–10 days which often are adverse to memory function [12]. After 10 days of exposure to D2 antagonist antipsychotics, the Class is shifted to a Class IV.

The dose of a drug is also important to the risk of delirium. The dose of each agent used on *LD* was compared to standard pharmacological sources [19,27]. **Dose level 1** was that dose that would not give therapeutic effect. **Dose level 2** was the common dose range felt to be therapeutic. **Dose level 3** is a dose which exceeds common dose ranges.

The DRN for a drug on a given day is calculated by multiplying the CLASS times the DOSE LEVEL. By example, doxepin 25 mg HS is a Class III drug but the dose is very low for the typical use as an antidepressant (100–250 mg per day for depression). Thus,

$$\text{DRN} = 3\ (\text{class III}) \times 1(\text{low dose level}) == 3$$

and for olanzapine 10 mg per day on the 12th day in a 74 year old male with low grade renal failure.

$$\text{DRN} = 4\ (\text{class IV}) \times 3(\text{high dose level for renal failure}) == 12$$

Table 1
Example DRN calculation

Patient: KC	Emer Dept	102Ptd	101Ptd	32Ptd	31Ptd	1Ptd
Haloperidol (III)	20 mg (3*4)					
Ziprasidone (III)				40 mg (+3*4)	40 mg (+3*4)	
Quetiapine (III)						400 mg (+4*4)
Risperidone (III)						0.5 mg (4*1)
Propranolol		180 mg (+1*3)	180 mg (+1*3)	20 mg (+1*1)	20 mg (+1*1)	Discontinued
Citalopram		20 mg (n/a)	20 mg (n/a)	Discontinued	Discontinued	Discontinued
FeSo4		325 mg (n/a)	325 mg (n/a)	150 mg (n/a)	150 mg (n/a)	Discontinued
Rivastigmine (-III)		9 mg (−3*2)	9 mg (−3*2)	Discontinued	Discontinued	Discontinued
Gabapentin (I)		300 mg (−1*1)		Discontinued	Discontinued	Discontinued
Doxepin (III)		1800 (−1*3)	1800 (−1*3)	Discontinued	Discontinued	Discontinued
Phosphatidylcholine		1800 (−1*3)	1800 (−1*3)	Discontinued	Discontinued	Discontinued
−DRN	0	9	9	0	0	0
+DRN	12	7	3	13	13	23
DRN Total	+12	−2	−6	+13	+13	+23

and for rivastigmine 9 mg per day

$$\text{DRN} = -3(\text{class -III}) \times$$
$$2\ (\text{therapeutic dose level}) == -6$$

The total daily DRN for the above three drugs is

$$\text{Daily DRN} = 3 + 12 - 6 = +9$$

Delirium threshold is a DRN of 5 for more than three days. This Case Study patient is at risk for delirium, especially if there is a pre-existing dementia.

Other examples of DRN calculation are given in Table 1. In the first column is the impact of an emergency department visit where haloperidol was used. The two shots of haloperidol gave a DRN load of 12, which exceeded the delirium threshold of five. A few days later (102–101 prio to death) the patient's DRN load was dropped to a negative 6 points. This allowed the delirium created in column one to clear. The fourth and fifth column (32–31 prior to death) display the prescribing impact of the hospitalist No2's hospitalists. Note that all anti-dementia drugs have been removed and propranolol was in process of being removed. The net result was a rise in DRN to 13 which exceeded the delirium threshold of five. The final column gives the patient's DRN calculation on the day prior to expiration. On this day, the DRN number has 23 which is four times the 'delirium threshold' of five.

Rating of delirium would be most accurately done prospectively [28]. However, in the present example the author has used retrospective review of the patient's five hospitalizations and periods in nursing facility. The Delirium Scale (dScale) used is simple and direct. It measures comments of nursing, physicians and other care provider's notes on a per day basis. Such measures have been shown to have high validity [29]. The advantage of this retrospective scale is the natural chart bias against the author's hypothesis that the medications were causal. The retrospective Delirium Scale is multiplied by 5 (dScalex5) so that it plots in the same range with the DRN. The criteria for the dScale:

0 = no evidence of delirium in record.
1 = minimum comments on confusion or uncooperativeness
2 = mild delirium with comments of unexpected confusion, actions, hallucinations or sleep disturbance
3 = agitation clearly commented on, substantial disruptive verbalization or uncooperativeness.
4 = extreme agitation, screaming for periods of time, striking out
5 = stupor, obtunded, or periods of lethargy punctuated by agitation
6 = medical crisis, arrhythmia, or coma

Figure 2 plots the DRN(Clear box) and dScalex5 (diamond pattern box) in four circumstances. Figure 2, "Plot A" is the five day average of 82 to 78 prior to death. This was under the care of the hospital No2's hospitalists. The DRN average was 7.8 and dScalex5 average was 12. The DRN was above the delirium threshold of five (double bar horizontal line). The dScalex5 of 12 implies the patient typically had moderate delirium with comments of unexpected confusion, agitation, hallucinations and or sleep disturbance. Tranquilizers and antipsychotics were used to control the patient. The patient was sent back to the nursing home before the full adverse effect of the tranquilizers and antipsychotics could be seen.

Figure 2, "Plot B" is of the authors care from 54 to 50prior to death. The average DRN was 0.8 and the dScalex5 was zero. Hence the dScalex5 did not appear on the graph. The DRN was far below the threshold of

delirium. No delirium or agitation was noted. Control of the agitation was accomplished by propranolol.

Figure 2, "Plot C" is a second period of care by the hospital No2's hospitalists. These data came from 35 to 31prior to death. The DRN was 7.2, which is above the delirium threshold. The dScalex5 was high at 21, which implies that the patient was displaying extreme agitation, screaming for periods of time, and striking out. Tranquilizers and antipsychotics were used to control the patient.

Figure 2, "Plot D" covers the final five days of LD's life. The five day average DRN was 20.8, which is four times the threshold of delirium. This is reflected by the dScalex5 of 23. The average daily dScale was 4.6. Clinically this would imply that the patient moves from extreme agitation, screaming for periods of time, and striking out; to stupor, obtunded, and periods of lethargy punctuated by agitation. A final comment in the chart was "*There were some reports that the patient did not eat much at dinner the night before, but otherwise there were no abnormal behaviors, complaints by the patient or abnormal vital signs.*" Per suggestion of the hospital No2's hospitalists, the staff at hospital No3 had simplified the regimen to increasing doses of quetiapine. Propranolol and anti-dementia drugs were removed entirely. On the day of death he was on 400 mg of quetiapine with 1 mg of risperidone given intramuscularly.

The actual cause of *LD*'s death will never be certain. It could have been from a fatal arrhythmia due to the quetiapine, as mentioned now in FDA black box labeling of such drugs [1]. It could also have been the LD slipped quietly from **alert wakefulness** to **obtundation** to intermittent **stupor** and **death** by respiratory depression from the increasing dosing with atypical antipsychotics. Such progression is classically described by Plum and Posner in *The Diagnosis of Stupor and Coma* [30].

3. Conclusion

The risk of administering antipsychotics to demented elderly patients, although not fully explored, is judged by the FDA to be substantial.

Propranolol is a safe and effective means to control the agitation of most frail elder agitated demented patient. The only contraindication is bronchospastic disease or known anaphylactic reactions. Dose finding can be time-consuming, because there is twenty-fold interindividual variation in dose response.

The case of LD, a 74 year old combative Alzheimer's patient, is one that offers clear comparison of the effect of propranolol versus antipsychotics and sedatives. The modified DRN method can be used to predict who is at risk of developing delirium.

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