Decreasing suicide risk with math

Dan Giurca, MD

Suicide is a common reality, accounting for approximately 800,000 deaths per year worldwide.[1] Properly assessing and minimizing suicide risk can be challenging. We are taught that lithium and clozapine can decrease suicidality, and many psychiatrists prescribe these medications with the firm, "evidence-based" belief that doing so reduces suicide risk. Paradoxically, what they in fact might be doing is the exact opposite; they may be giving high-risk patients the opportunity and the means to attempt suicide with a lethal amount of medication.

One patient diagnosed with a mood disorder who attempted suicide had a surprising point of view. After taking a large quantity of lithium in an attempt to overdose, she was admitted to the psychiatry unit. Upon discharge, the doctors gave her another handful of pills. She reported feeling that her physicians were giving her the means to attempt suicide again. This mindset forced me to rethink suicide risk, and I approached it as a math problem.

Operations research is a subfield of mathematics that tries to optimize one or more variables when multiple variables are in play. One example would be to maximize profit while minimizing cost. During World War II, operations research was used to decrease the number of munitions used to shoot down airplanes, and to sink submarines more efficiently.

Focusing on the patient who attempted suicide by overdose, the question was: If she was discharged from the psychiatry unit with a 30-day supply of medication, how lethal would that prescription be if deliberately taken all at once? And what can be done to minimize this suicide risk? Psychiatrists know that some medications are more dangerous than others, but few have performed quantitative analysis to determine the potential lethality of these medications. The math analysis did not involve multivariable calculus or differential equations, only multiplication and division. The results were eye-opening.

Calculating relative lethality

The lethal dose 50 (LD50) is the dose of a medication expressed in mg/kg that results in the death of 50% of the animals (usually rats) used in a controlled experiment. Open-source data for the LD50 of medications is provided by the manufacturers.

I tabulated this data for a wide range of psychiatric medications, including antipsychotics, mood stabilizers, and selective serotonin reuptake inhibitors, in a spreadsheet with columns for maximum daily dose, 30-day supply of the medication, LD50 in mg/kg, LD50 for a 60-kg subject, and percentage of the 30-day supply compared with LD50. I then sorted this data by relative lethality (for my complete data, see the ***Figure*** and ***Table*** at CurrentPsychiatry.com).

continued

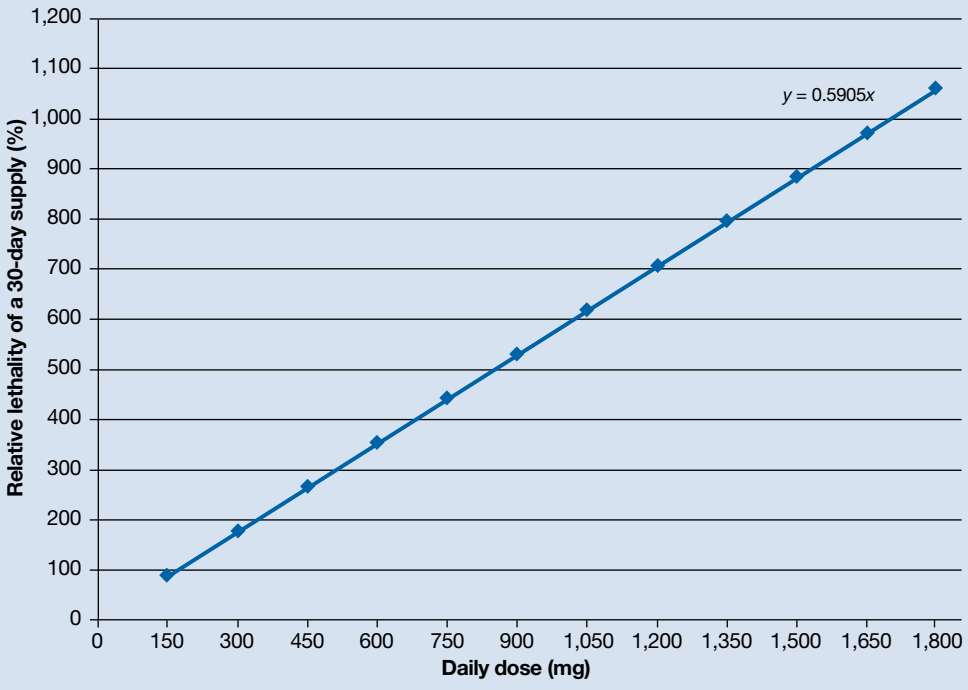
Dr. Giurca is Director, Consultation-Liaison Psychiatry, and Assistant Clinical Professor of Psychiatry, Orange Regional Medical Center, Middletown, New York.

Disclosure

The author reports no financial relationship with any company whose products are mentioned in this article or with manufacturers of competing products.

Figure

Relative lethality of lithium



Note: Human equivalent dose was derived from rat lethal dose 50 using FDA conversion factor 6.2 to account for differences in metabolism and body surface area of a 60-kg person; this was used to calculate the relative lethality of a 30-day prescription given to a patient.

Relative lethality of commonly prescribed psychiatric medications varies tremendously

The rat dose in mg/kg was extrapolated to the human equivalent dose (HED) in mg/kg using a conversion factor of 6.2 (for a person who weighs 60 kg, the HED = LD50/6.2) as suggested by the FDA.[2] The dose for the first fatality is smaller than the HED, and toxicity occurs at even smaller doses. After simplifying all the terms, the formula for the HED-relative lethality is $f(x) = \frac{310}{LD50} \times x$, where x is the daily dose of a medication prescribed for 30 days. This is the equation of a straight line with a slope inversely proportional to the LD50 of each medication and a y-axis intercept of 0. Each medication line shows that any dose rising above 100% on the y-axis is a quantum higher than the lethal dose.

Some commonly prescribed psychotropics are highly lethal

The relative lethality of many commonly prescribed psychiatric medications, including those frequently used to reduce suicidality, varies tremendously. For example, it is widely known that the first-line mood stabilizer lithium has a narrow therapeutic window and can rapidly become toxic. If a patient becomes dehydrated, even a normal lithium dose can be toxic or lethal. Lithium has a relative lethality of 1,063% (***Figure***). Clozapine has a relative lethality of 1,112%. Valproic acid has an even higher relative lethality of 1,666%. By contrast, aripiprazole and olanzapine have a relative lethality of 10% and 35%, respectively. For preventing suicide, prescribing a second-generation antipsychotic with a lower relative lethality may be preferable over prescribing a medication with a higher relative lethality.

According to U.S. poison control centers,[3] from 2000 to 2014, there were 15,036 serious outcomes, including 61 deaths, associated with lithium use, and 6,109 serious outcomes, including 37 deaths, associated with valproic acid. In contrast, there were

Discuss this article at www.facebook.com/CurrentPsychiatry

only 1,446 serious outcomes and no deaths associated with aripiprazole use.[3] These outcomes may be underreported, but they are consistent with the mathematical model predicting that medications with a higher relative lethality will have higher morbidity and mortality outcomes, regardless of a patient's intent to overdose.

Many psychiatrists have a preferred antidepressant, mood stabilizer, or antipsychotic, and may prescribe this medication to many of their patients based on familiarity with the agent or other factors. However, simple math can give the decision process of selecting a specific medication for a given patient a more quantitative basis.

Even a small reduction in suicide would save many lives

Ultimately, the math problem comes down to 4 minutes, which is approximately how long the brain can survive without oxygen. By prescribing medications with a lower relative lethality, or by prescribing a less-than-30-day supply of the most lethal medications, it may be possible to decrease overdose morbidity and mortality, and also buy enough time for emergency personnel to save a life. If simple math can put even a 1% dent in the rate of death from suicide, approximately 8,000 lives might be saved every year.

Acknowledgments

Psychiatry residents Christopher Walfall, DO, Ryan Omura, DO, contributed in collecting the open-source LD50 data for the project; medical student Alice Jiang, OMS-IV, helped with the creation of the spreadsheet.

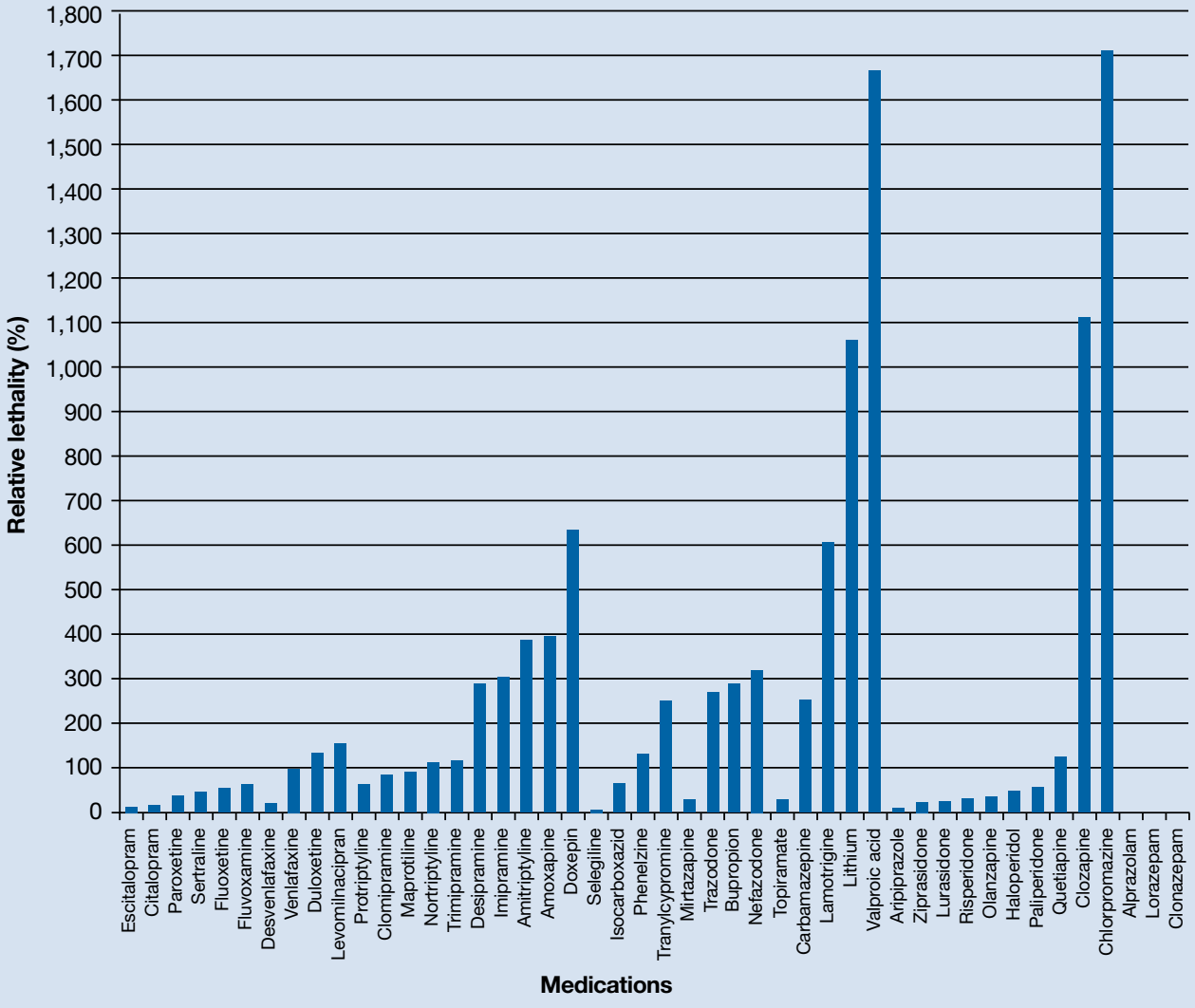
References

1. World Health Organization. Suicide. Fact sheet. http://www.who.int/mediacentre/factsheets/fs398/en. Updated August 2017. Accessed January 3, 2018.
2. U.S. Food and Drug Administration. Estimating the maximum safe starting dose in initial clinical trials for therapeutics in adult healthy volunteers. https://www.fda.gov/downloads/drugs/guidances/ucm078932.pdf. Published July 6, 2005. Accessed January 8, 2018.
3. Nelson JC, Spyker DA. Morbidity and mortality associated with medications used in the treatment of depression: an analysis of cases reported to U.S. Poison Control Centers, 2000-2014. Am J Psychiatry. 2017;174(5):438-450.

Simple math can give the decision process of selecting specific medications for a patient a more quantitative basis

Figure

HED relative lethality of psychiatric medications



HED: human equivalent dose

Note: HED was derived from rat lethal dose 50 using FDA conversion factor 6.2 to account for differences in metabolism and body surface area of a 60-kg person.

Table

LD50 data and relative lethality for commonly prescribed psychiatric medications

Type	Max daily dose (mg)	30-day supply (mg)	LD50 (mg/kg)	Weight (kg)	LD50 (mg)	Relative lethality 1 (%)	HED (mg)	Relative lethality 2 (%)
SSRIs								
Escitalopram	20	600	980	60	58,800	1.02	9,484	6.33
Citalopram	40	1,200	800	60	48,000	2.50	7,742	15.50
Paroxetine	50	1,500	415	60	24,900	6.02	4,016	37.35
Sertraline	200	6,000	1,327	60	79,620	7.54	12,842	46.72
Fluoxetine	80	2,400	452	60	27,120	8.85	4,374	54.87
Fluvoxamine	300	9,000	1,500	60	90,000	10.00	14,516	62.00
SNRIs								
Desvenlafaxine	50	1,500	700	60	42,000	3.57	6,774	22.14
Venlafaxine	225	6,750	700	60	42,000	16.07	6,774	99.64
Duloxetine	120	3,600	279	60	16,740	21.51	2,700	133.33
Levomilnacipran	120	3,600	238	60	14,280	25.21	2,303	156.30
TCAs								
Protriptyline	60	1,800	299	60	17,940	10.03	2,894	62.21
Clomipramine	250	7,500	914	60	54,840	13.68	8,845	84.79
Maprotiline	225	6,750	760	60	45,600	14.80	7,355	91.78
Nortriptyline	150	4,500	405	60	24,300	18.52	3,919	114.81
Trimipramine	300	9,000	800	60	48,000	18.75	7,742	116.25
Desipramine	300	9,000	320	60	19,200	46.88	3,097	290.63
Imipramine	300	9,000	305	60	18,300	49.18	2,952	304.92
Amitriptyline	300	9,000	240	60	14,400	62.50	2,323	387.50
Amoxapine	400	12,000	313	60	18,780	63.90	3,029	396.17
Doxepin	300	9,000	147	60	8,820	102.04	1,423	632.65
MAOIs								
Selegiline	10	300	385	60	23,100	1.30	3,726	8.05
Isocarboxazid	60	1,800	280	60	16,800	10.71	2,710	66.43
Phenelzine	90	2,700	210	60	12,600	21.43	2,032	132.86
Tranylcypromine	60	1,800	75	60	4,500	40.00	726	248.00
OTHER ANTIDEPRESSANTS								
Mirtazapine	45	1,350	490	60	29,400	4.59	4,742	28.47
Trazodone	600	18,000	690	60	41,400	43.48	6,677	269.57
Bupropion	450	13,500	482	60	28,920	46.68	4,665	289.42
Nefazodone	600	18,000	582	60	34,920	51.55	5,632	319.59
MOOD STABILIZERS								
Topiramate	400	12,000	3,745	60	224,700	5.34	36,242	33.11
Carbamazepine	1,600	48,000	1,957	60	117,420	40.88	18,939	253.45
Lamotrigine	400	12,000	205	60	12,300	97.56	1,984	604.88
Lithium	1,800	54,000	525	60	31,500	171.43	5,081	1,062.86
Valproic acid	3,600	108,000	670	60	40,200	268.66	6,484	1,665.67
ANTIPSYCHOTICS								
Aripiprazole	30	900	953	60	57,180	1.57	9,223	9.76
Ziprasidone	160	4,800	2,000	60	120,000	4.00	19,355	24.80
Lurasidone	120	3,600	1,320	60	79,200	4.55	12,774	28.18
Risperidone	6	180	57	60	3,420	5.26	552	32.63
Olanzapine	20	600	177	60	10,620	5.65	1,713	35.03
Haloperidol	20	600	128	60	7,680	7.81	1,239	48.44
Paliperidone	12	360	65	60	3,900	9.23	629	57.23
Quetiapine	800	24,000	2,000	60	120,000	20.00	19,355	124.00
Clozapine	900	27,000	251	60	15,060	179.28	2,429	1,111.55
Chlorpromazine	800	24,000	145	60	8,700	275.86	1,403	1,710.34
ANXIOLYTICS								
Alprazolam	4	120	3,100	60	186,000	0.06	30,000	0.40
Lorazepam	10	300	4,500	60	270,000	0.11	43,548	0.69
Clonazepam	20	600	4,000	60	240,000	0.25	38,710	1.55

Note: Dose conversion from rat to human (human equivalent dose); model 1 based on mg/kg conversion; model 2 based on FDA correction with conversion factor 6.2. Lurasidone LD50 listed as range 1,320 to 6,690 mg/kg by Sigma-Aldrich, with 1,320 mg/kg used for calculations. Sunovion reports no rat deaths at 2,000 mg/kg but 1,320 mg/kg was used for calculations. Ziprasidone LD50 >2,000 mg/kg as per Pfizer, but 2,000 mg/kg was used for calculations.

HED: human equivalent dose; LD50: lethal dose 50; MAOI: monoamine oxidase inhibitor; SNRI: serotonin-norepinephrine reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor; TCA: tricyclic antidepressant