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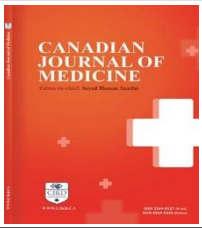

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Understanding and Using the Variable Therapeutic Region of Lithium for Bipolar Patients During Aging

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ABSTRACT

In 2019, Shulman et al. [1] summarized the known lithium therapeutic ranges for Old Age Bipolar Patients (OABP). For patients over 60, the range is 0.4-0.8 mmol/L, and for those over 80, 0.4-0.7 mmol/L. For younger patients, the standard region is 0.6-1.2 mmol/L. The current research leaves three disconnected therapeutic ranges. A unifying theory is developed explaining the therapeutic range of lithium for all ages. It explains why the changes in the therapeutic range happen and exactly how the upper limits change on a year by year basis instead of by decades. It also explains why and when the standard therapeutic range should be abandoned. In developing the theory, only information about the changes with age in the eGFR is used; when applied to lithium, the theory explains why the therapeutic regions for over sixty and over eighty exist. The known ranges were discovered using empirical evidence. The theory gives a more precise start for those regions as well as how to move smoothly through them. It applies for bipolar patients who do not have chronic kidney disease and shows that a new therapeutic region for those over 90 needs to be created. Table 1 is developed using the new theory to give the upper limit, the midpoint, and the twenty-fifth percentile up from the minimum level of the therapeutic range for each year from age fifty to one hundred. This table enables doctors to keep the patient's serum level where they want it as the patient ages.

Background

For decades the accepted therapeutic range of lithium had been 0.6-1.2 mmol/L. Many doctors recognised that, as people aged, the target level should gradually be lowered. In 2005, Young [2] reported that, for the aged, the range should be 0.5-1.0 mmol/L. In 2010, Shulman [3] reported that, for age greater than 75 years, lithium levels exceeding 0.8 mmol/L

are likely to produce significant adverse effects or toxicity. In 2019, Shulman et al. [1] reported that, for patients over 60, the therapeutic range should be 0.4-0.8 mmol/L, with toxic symptoms appearing above 0.8 mmol/L, and for over 80, the therapeutic range decreases to 0.4-0.7 mmol/L.

Historically, many doctors thought they were being safe by keeping the patient's blood level at or just below 0.9 mmol/L, the midpoint of the standard therapeutic range. Doctors kept using this target blood serum level regardless of the patient's age. It's well known that as the patient ages, the lithium dose needs to be reduced to maintain the blood serum level at a safe level because the therapeutic range shrinks with age.

Method

In Graph 1, the therapeutic ranges for all three known therapeutic ranges are presented. Note the gap in the graph at ages 40 and 50.

Graph 1. Therapeutic ranges (###) and toxic ranges (xxx) for various ages and blood serum levels

Age	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1.0	1.1	1.2	1.3	1.4	1.5
110				###	###	###	###	xxx							
100				###	###	###	###	xxx							
90				###	###	###	###	xxx							
80				###	###	###	###	xxx							
70				###	###	###	###	###	xxx						
60				###	###	###	###	###	xxx						
50															
40															
30							###	###	###	###	###	###			xxx
20							###	###	###	###	###	###			xxx
10							###	###	###	###	###	###			xxx
0							###	###	###	###	###	###			xxx

Blood serum level

We will now develop a general theory that explains why and how the therapeutic range changes with age. The theory also provides doctors with a simple way of dealing with the changes in the therapeutic range as patients age.

The lithium blood serum level for a patient on any dose of lithium is dependent on the functionality of the kidneys. Kidneys slowly become less efficient with age even for people who do not have chronic kidney disease. The eGFR (estimated glomerular filtration rate) is a good indicator of kidney's function, and its change with age is well-known. We will use the table of accepted ranges for eGFR to develop the necessary theory. Table 1 shows average eGFR for age ranges by decade (Source: National Kidney Society).

Table 1. eGFR range by age

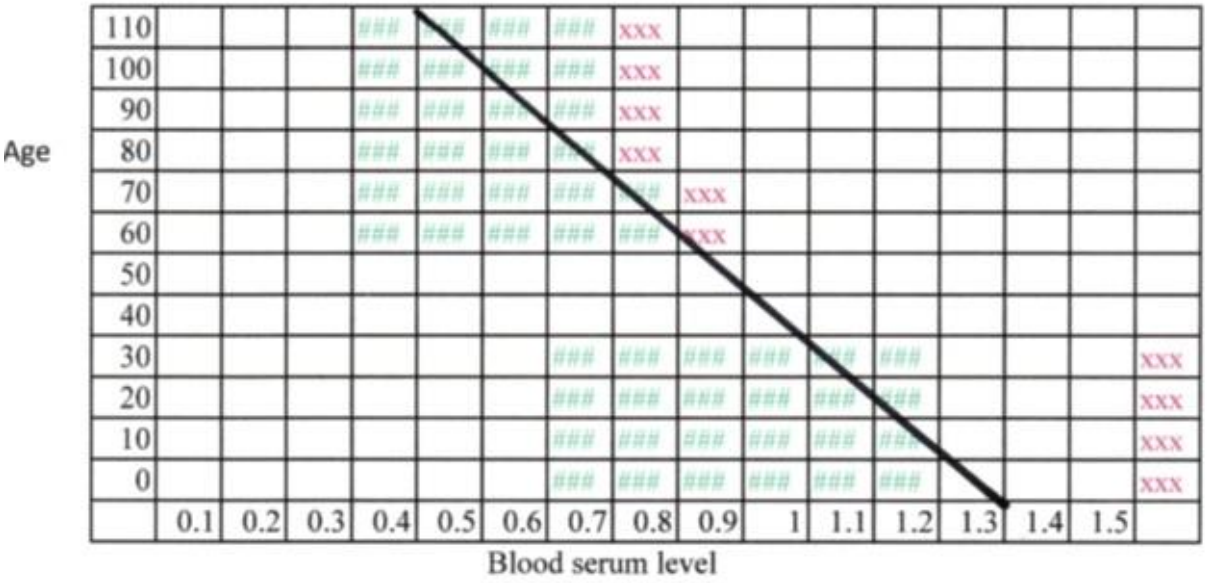
Age in years	Average eGFR
20-29	116
30-39	107
40-49	99
50-59	93
60-69	85
70 and older	75

A linear regression on the data in Table 1 gives the following equation for the eGFR changes.

Equation 1: eGFR = 131 - 0.79*Age

To try to plot the regression line generated by equation 1 on Graph 1 would be like comparing apples to oranges. However, if the regression line is scaled by dividing all points on the line by 100, the line can be added to Graph 1 to get Graph 2.

Graph 2. Therapeutic ranges (###) and toxic ranges (xxx) for various ages and blood serum levels with regression line



Note. The bottom axis of Graph 2 stands for both the blood serum level and the eGFR/100.

The regression line was developed without using any information about the lithium therapeutic regions that have been discovered using empirical data. When the scaled equation is overlaid in Graph 2 (the thick line), it predicts that the therapeutic range is near 0.8 at age 60 and reaches 0.8 at age 65. This matches known empirical results. The scaled line predicts the maximum level of the therapeutic region at age 80 is 0.7, which matches exactly the empirically developed therapeutic region. The empirically developed therapeutic ranges are predicted by the theoretical result, which verifies that the theory is correct. The theory can be used for more detailed predictions of the therapeutic regions for OABP.

For eGFR 90 or above, the kidney function is normal; below that, there is some loss of kidney function (Source: National Kidney Society). By using equation 1, it can be determined that a person's eGFR drops to 90 at about age 52. This means that the standard therapeutic range can be used until a person is 52 years old. After that age, the standard therapeutic range should be abandoned. Graph 2 has part of the therapeutic range for the standard region past the regression line. Most doctors keep the maintenance dose of lithium at, or below 0.9, the midpoint of the standard therapeutic region. The regression line indicates that the top of the blood serum therapeutic range at age 52 is 0.9, which means that for most patients the maintenance dose keeps them below the regression line until age 52. In the seven years of treatment from age 52 to age 60, the blood serum level should be gradually reduced to reach level 0.84 or less if the patient's maintenance dose is not already at that level.

After age 50, the natural decrease in kidney function means that the therapeutic range must be continuously reduced to avoid lithium toxicity. The theory developed in this paper has the following rules:

Rule one: for patients younger than 50, the standard therapeutic region should be used to keep the blood serum level below the midpoint of blood level 0.9 and preferable in the bottom part of the therapeutic region.

Rule two: the lower level of the therapeutic range will be fixed at 0.4 for patients older than 50.

Rule three: for patients older than 50, the scaled regression line for the eGFR decay is used as the guideline for the upper limit of the therapeutic range.

It would be difficult for doctors to keep using equation 1 to calculate the required blood serum levels on a year by year basis. To give doctors a tool for managing the lithium dose as the patient ages, Table 2 is created using the theory developed. The entry for 25% in Table 2 is the 25^{th} percentile of the therapeutic region.

Table 2. Maximum, Midpoint, and 0.25th percentile of the therapeutic range by Age

Age	50	51	52	53	54	55	56	57	58	59
Top	0.92	0.91	0.90	0.89	0.88	0.88	0.87	0.86	0.85	0.84
midpoint	0.66	0.65	0.65	0.65	0.64	0.64	0.63	0.63	0.63	0.62
25%	0.53	0.53	0.52	0.52	0.52	0.52	0.52	0.51	0.51	0.51

Age	60	61	62	63	64	65	66	67	68	69
Top	0.84	0.83	0.82	0.81	0.80	0.80	0.79	0.78	0.77	0.76
midpoint	0.62	0.61	0.61	0.61	0.60	0.60	0.59	0.59	0.59	0.58
25%	0.51	0.51	0.51	0.50	0.50	0.50	0.50	0.50	0.49	0.49

Age	70	71	72	73	74	75	76	77	78	79
Top	0.76	0.75	0.74	0.73	0.73	0.72	0.71	0.70	0.69	0.69
midpoint	0.58	0.57	0.57	0.57	0.56	0.56	0.55	0.55	0.55	0.54
25%	0.49	0.49	0.49	0.48	0.48	0.48	0.48	0.48	0.47	0.47

Age	80	81	82	83	84	85	86	87	88	89
Top	0.68	0.67	0.66	0.65	0.65	0.64	0.63	0.62	0.61	0.61
midpoint	0.54	0.54	0.53	0.53	0.52	0.52	0.52	0.51	0.51	0.50
25%	0.47	0.47	0.47	0.46	0.46	0.46	0.46	0.46	0.45	0.45

Age	90	91	92	93	94	95	96	97	98	99
Top	0.60	0.59	0.58	0.58	0.57	0.56	0.55	0.54	0.54	0.53
midpoint	0.50	0.50	0.49	0.49	0.48	0.48	0.48	0.47	0.47	0.46
25%	0.45	0.45	0.45	0.44	0.44	0.44	0.44	0.44	0.43	0.43

As presented in Table 2, the therapeutic range for OABP is shown year by year, which allows for smoothly moving through the necessary blood level reductions.

Results

Graph 3 shows the complete therapeutic region developed in this paper, including the eGFR line that controls the upper limit of the region as the patient ages.

Graph 3. Therapeutic ranges ###, and toxic ranges xxx for various ages and blood serum levels with regression line

Graph 3 shows that the previously reported separate therapeutic regions, each with its own fixed upper blood level, need to be replaced by the values in Graph 3. Because the eGFR decreases a little more each year, after age 50, the therapeutic range shrinks a little more each year.

Doctors can use Table 2 to determine the therapeutic range, the midpoint, and the 25th percentile point for individual patients as they age. Using the results from Table 2, the top of the therapeutic range at age 90 has a blood serum level of 0.6. This means that all patients age 90 or older must have a blood serum level at or below 0.6. This very specific result from the mathematical model predicts the more general results of Bocchetta et al. [4] who reported that the therapeutic range for the very elderly is below the standard range used for younger adults. Blood serum levels less than 0.6mmol/L are needed for the very elderly.

Conclusions

A theory as to why and how the therapeutic range alters year by year for patients older than 50 has been developed. The therapeutic range for lithium is not a set of regions each with a fixed upper limit for the therapeutic range. It has been shown that the therapeutic upper limit for the blood serum level decreases in a smooth, predictable, linear way, as the patient ages. Uncertainty about the therapeutic range for a bipolar patient on lithium has been removed. The standard therapeutic range should stop being used when a patient reaches age 50.

Table 2 allows doctors to easily know what the target lithium blood level should be, on a year by year basis, for OABP. The table contains the upper level, the midpoint level, and the 25th percentile level of the therapeutic region for each year from age 50 to 100.

The theory is particularly useful for the very elderly. Table 2 shows at what age the upper therapeutic level limit reduces to 0.6 mmol/L. In addition, Table 2 shows how the upper limit of lithium changes up to age 100 and can easily be extended using the method of the paper.

Declarations

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