Clinical and Practical **Psychopharmacology**

Understanding Relative Risk, Odds Ratio, and Related Terms:
As Simple as It Can Get

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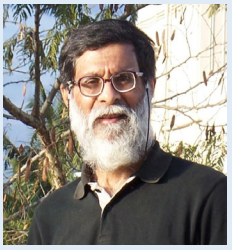

Each month in his online column, Dr Andrade considers theoretical and practical ideas in clinical psychopharmacology with a view to update the knowledge and skills of medical practitioners who treat patients with psychiatric conditions.

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ABSTRACT

Risk, and related measures of effect size (for categorical outcomes) such as relative risks and odds ratios, are frequently presented in research articles. Not all readers know how these statistics are derived and interpreted, nor are all readers aware of their strengths and limitations. This article examines several measures, including absolute risk, attributable risk, attributable risk percent, population attributable risk percent, relative risk, odds, odds ratio, and others. The concept and method of calculation are explained for each of these in simple terms and with the help of examples. The interpretation of each is presented in plain English rather than in technical language. Clinically useful notes are provided, wherever necessary.

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Introduction

Many research papers present findings as odds ratios (ORs) and relative risks (RRs) as measures of effect size for categorical outcomes. Whereas these and related terms have been well explained in many articles,[1–5] this article presents a version, with examples, that is meant to be both simple and practical. Readers may note that the explanations and examples provided apply mostly to randomized controlled trials (RCTs), cohort studies, and case-control studies. Nevertheless, similar principles operate when these concepts are applied in epidemiologic research. Whereas the terms may be applied slightly differently in different explanatory texts, the general principles are the same.

Clinical Situation

Consider a hypothetical RCT in which 76 depressed patients were randomly assigned to receive either venlafaxine (n = 40) or placebo (n = 36) for 8 weeks. During the trial, new-onset sexual dysfunction was identified in 8 patients treated with venlafaxine and in 3 patients treated with placebo. These results are presented in Table 1. Using these data, we can calculate the values for a variety of terms, as illustrated in the sections that follow.

Absolute Risk

Concept. The absolute risk of an event is the likelihood of occurrence of that event in the population at risk.

Calculation. The absolute risk of an event is estimated as the number of persons who actually experience the event divided by the total number of persons exposed to the risk of that event. This figure is usually expressed as a percentage, though it can also be expressed in other ways, such as per 1,000 or per 100,000 persons in the population at risk. It can also be expressed in terms of person-years of exposure to the risk factor.

Worked example. Using the data in Table 1, because 40 patients took venlafaxine and because 8 of them developed sexual dysfunction, the absolute risk of sexual dysfunction with venlafaxine is 8/40, or 20.0%. Similarly, the absolute risk of developing sexual dysfunction with placebo is 3/36, or 8.3%.

Expressed in plain English, 20.0% of patients who receive venlafaxine (as administered in this trial) and 8.3% of those who receive placebo (as administered in this trial) can expect to experience new-onset sexual dysfunction during the first 8 weeks of treatment. Presumably, sexual dysfunction resulting from venlafaxine treatment involves specific drug-related mechanisms, whereas sexual dysfunction with placebo involves nocebo mechanisms, illness-related factors, or other causes.

Attributable Risk or Risk Difference

Concept. The attributable risk is the risk of an event that is specifically due to the risk factor of interest.

Clinical Points

- The absolute risk is the probability of an event in a sample or population of interest. The relative risk (RR) is the risk of the event in an experimental group relative to that in a control group. The odds ratio (OR) is the odds of an event in an experimental group relative to that in a control group.
- An RR or OR of 1.00 indicates that the risk is comparable in the two groups. A value greater than 1.00 indicates increased risk; a value lower than 1.00 indicates decreased risk. The 95% confidence intervals and statistical significance should accompany values for RR and OR.
- RR and OR convey useful information about the effect of a risk factor on the outcome of interest. However, the RR and OR must be interpreted in the context of the absolute risk as well as the clinical importance of the outcome in the individual patient.

Calculation. It is estimated as the difference in the absolute risk (of the event of interest) between persons exposed to the risk factor and persons not exposed to the risk factor. It is usually expressed as a percentage.

Worked example. Using the data in Table 1, the risk of sexual dysfunction attributable specifically to venlafaxine is the absolute risk of sexual dysfunction with venlafaxine minus that with placebo; that is, 20.0% – 8.3%, or 11.7%.

Expressed in plain English, 20% of patients who receive venlafaxine (as administered in this trial) can expect to develop sexual dysfunction. However, in only 11.7% of the patients is the adverse event specifically attributable to venlafaxine; in the remaining 8.3%, other causes are probably responsible (eg, nocebo mechanisms, illness-related factors).

Clinical note. The reciprocal of the attributable risk yields the number-needed-to-treat/harm statistic.[6]

Attributable Risk Percent

Concept. The attributable risk percent is the percentage of cases (in whom the event of interest occurs) in the population at risk (ie, persons exposed to the risk factor of interest) that is specifically attributable to the risk factor of interest. This statistic is not commonly used in the context of RCTs; however, it assumes importance in epidemiologic studies and in public health planning.

Calculation. It is estimated as the attributable risk divided by the absolute risk, converted to a percentage.

Worked example. In the previous section, we observed that 11.7% out of the overall 20.0% risk (of sexual dysfunction with venlafaxine) is specifically attributable to venlafaxine. So, the attributable risk percent for venlafaxine is (11.7%/20.0%) × 100; that is, 58.5%.

Expressed in plain English, whatever the actual number of cases of sexual dysfunction detected with venlafaxine in the population, only 58.5% of this number would have sexual dysfunction that is specifically due to venlafaxine; in the remaining cases (41.5%), other explanations are likely (eg, nocebo mechanisms, illness-related factors).

Table 1. Hypothetical Results of an 8-Week Randomized Controlled Trial of Venlafaxine (n = 40) vs Placebo (n = 36)

	Developed Sexual Dysfunction	Did Not Develop Sexual Dysfunction	Total
Received venlafaxine	8	32	40
Received placebo	3	33	36
Total	11	65	76

Population Attributable Risk Percent

Concept. The population attributable risk percent is the percentage of cases (in whom the event of interest occurs) in the general population (that is, regardless of exposure to the risk factor of interest) that is specifically attributable to the risk factor of interest. Otherwise expressed, it is the percentage of cases that would be eliminated from the general population were the risk factor to be eliminated.

This statistic is not used in the context of RCTs; however, it assumes importance in epidemiologic studies and other population-based studies. The statistic is of particular interest to persons involved in planning and public health.

Calculation. It is estimated as the attributable risk multiplied by the prevalence of the risk factor in the population; the result is expressed as a percentage.

Worked example. Suppose that 0.5% of the population uses venlafaxine. In an earlier section, we estimated that the risk of sexual dysfunction specifically attributable to venlafaxine was 11.7%. Therefore, 11.7% of 0.5% of the population will experience sexual dysfunction specifically attributable to venlafaxine. This is calculated as 11.7% × 0.5%; expressed as a percentage, the value is nearly 0.06%.

Expressed in plain English, 0.06% of the general population is likely to suffer from venlafaxine-related sexual dysfunction. Thus, this statistic tells us about the contribution of venlafaxine to sexual dysfunction in the general population.

Using this statistic, Rai et al[7] showed that even if antidepressant use during pregnancy is etiologically responsible for the development of autism spectrum disorders in the offspring, avoidance of antidepressant use during pregnancy would prevent only 0.6% of autism spectrum disorder cases.

Relative Risk

Concept. The relative risk (RR) of an event is the likelihood of its occurrence after exposure to a risk variable as compared with the likelihood of its occurrence in a control or reference group.

Calculation. The RR is estimated as the absolute risk with the risk variable divided by the absolute risk in the control group. It is almost invariably expressed as a ratio to denominator 1 rather than as a percentage.

Worked example. With reference to the data in Table 1, the absolute risks of sexual dysfunction with venlafaxine and placebo are 20.00% and 8.33%, respectively. The RR is therefore 20.00/8.33, or 2.40.

Expressed in plain English, venlafaxine, relative to placebo, is associated with a 2.4-fold increased risk of sexual dysfunction. This can also be stated in several other ways:

- Venlafaxine is associated with a more than doubled risk of sexual dysfunction.
- The risk of sexual dysfunction with venlafaxine is 2.4 times that with placebo.
- The risk of sexual dysfunction with venlafaxine is 240% that with placebo.
- Venlafaxine is associated with a 1.4-fold increase in the risk of sexual dysfunction.
- Venlafaxine is associated with a 140% increase in the risk of sexual dysfunction.
  (An explanatory note here: Why 1.4 and 140%? Because an RR of 2.4 means "2.4/1," or 2.4 cases with venlafaxine for every case with placebo. In other words, there are 1.4 extra cases with venlafaxine for every case with placebo; 1.4 and 140% are synonymous.)

Some of these ways of expressing the finding sound more alarming than others, and authors may manipulate the reader by using more or less alarming phraseology to increase or decrease the emotional impact of their finding.

Points to note:

1. *Risk* and *relative risk* are terms the use of which is not limited to adverse outcomes; for example, one may compare the "risk" of response and remission with venlafaxine with the "risk" of response and remission with placebo to obtain an RR that indicates, as a hypothetical example, that venlafaxine is associated with an 80% increase in the "risk" of response and a 60% increase in the "risk" of remission. Risk, therefore, is used to reflect probability, regardless of the desirability or undesirability of an event.
2. *Relative risk* is an important and commonly used term. An RR of 1.00 means that the risk of the event is identical in the exposed and control samples. An RR that is less than 1.00 means that the risk is lower in the exposed sample. An RR that is greater than 1.00 means that the risk is increased in the exposed sample.
3. An RR of, say, 0.3 can be expressed in plain English in many ways. It indicates that the risk is lowered to less than one-third; that the risk is reduced to 30%, that the risk is lowered by more than two-thirds, and that the risk is reduced by 70%. The reduction is from 1.00 (or from 100%, which is mathematically the same as 1.00).
4. As a measure of effect size, an RR value is generally considered clinically significant if it is less than 0.50 or more than 2.00; that is, if the risk is at least halved, or more than doubled. However, RR values that are closer to 1.00 can also be considered clinically significant if the event is serious or if it is important to public health.[5]
5. The statistical significance of an RR value is usually provided. It is possible for an RR value to be well below 1.00, or well above 1.00, and yet not statistically significant, and it is possible for an RR value to be very close to 1.00 (ie, probably not clinically significant) but yet statistically significant because the study was conducted on a large sample.
6. RR values are accompanied by their 95% confidence intervals (CIs). The statistical significance of an RR value can be inferred from the 95% CI.[8] If the CI includes the value 1.00, the RR is not statistically significant. For example, if the RR is 1.70 and the CI is 0.90–2.50, then the elevation in risk is not statistically significant because the value 1.00 (no difference in risk) lies within the range of the confidence interval.
7. The comparison, reference, or control group for RR calculation can be any group that is a valid control for the exposure of interest. For the venlafaxine study (Table 1), the comparison group received placebo; had it received another antidepressant drug, the RR would tell us by how much venlafaxine increased or decreased the risk of sexual dysfunction relative to that antidepressant. In a study examining the risk of schizophrenia, the exposure group could be persons with a positive family history and the control group, those with a negative family history. In a study of the effects of diet on a health outcome, the exposure group could comprise persons in the highest quintile for exposure to a nutrient variable, and the control group could comprise those in the lowest quintile.

Odds Ratio

Concept of odds. The odds of an event is a ratio of the frequency (or likelihood) of its occurrence to the frequency (or likelihood) of its nonoccurrence. Thus, the *odds* of rolling 6 with a die are 1 to 5 (ie, 0.20); this contrasts with the *risk* of rolling 6, which is 1/6 (ie, 0.17). Similarly, the odds of tossing heads with a coin are 1 to 1 (or "50-50," or 1.00), whereas the risk of tossing heads is 1/2 or 0.5.

Concept of odds ratio. The OR is a comparison of the odds of an event after exposure to a risk factor with the odds of that event in a control or reference situation.

Calculation. The OR is estimated as the odds of an event in the exposure group divided by the odds of that event in the control or reference group; the result is expressed as a ratio to denominator 1.

Worked example. With reference to the data in Table 1, the odds of developing sexual dysfunction with venlafaxine are 8:32 (ie, 8/32, or 0.25), and the odds of developing sexual dysfunction with placebo are 3:33 (ie, 3/33, or 0.091). The OR, therefore, is 8:32/3:33, or 2.75.

Expressed in plain English, the odds of developing sexual dysfunction with venlafaxine (relative to placebo) are 2.75 to 1.

Points to note:

1. The OR is numerically different from the RR, even though both seek to compare the same risk between the same groups. This is because the 2 statistics are based on different underlying concepts, as the worked examples in this and earlier sections show.
2. ORs and RRs are similar when the event being assessed is rare in the control group (or population).[9] However, ORs can substantially overestimate (if > 1.00) or underestimate (if < 1.00) RRs when the event is common.[10] ORs are also less easy to express in plain English, and hence less easy to understand, than RRs. For these and other reasons, wherever possible, RRs should be estimated rather than ORs.[10,11] So, why or when should ORs continue to be used? Answers are provided in the next section.
3. The relationship between the OR and RR is nonlinear, but mathematical methods exist to convert ORs to RRs.[9]
4. ORs are interpreted in the same way as RRs. An OR of 1.00 means that there is no increase or decrease in risk. An OR that is < 1.00 means that exposure to the risk variable reduces the risk of the event. An OR that is > 1.00 means that the risk is increased. The statistical significance of an OR is stated along with the OR and its 95% CI. If the 95% CI for the OR includes 1.00, the OR is not statistically significant.
5. How does one express an OR of 0.15 in plain English? Had this been an RR, we would have said that the intervention reduced the risk by 85%. Because it is an OR, we must say that for every 0.15 (or 15) persons who experience the event in the experimental group, 1 person (or 100 persons) will experience the event in the control group. That is, the odds are 15 to 100.

When Is It Reasonable to Compute Odds Ratios?

There are 2 principal situations in which the computation of ORs is justified:

1. In case-control studies, where the absolute risks and hence the relative risks cannot be estimated.
2. In logistic regression analyses, where ORs are generated as part of the analysis.

Consider a case-control study in which outpatients with depression were cross-sectionally screened for the presence of sexual dysfunction. For each patient who had sexual dysfunction, 6 age- and sex-matched depressed controls (without sexual dysfunction) were identified. Cases (n = 11) and controls (n = 65) were asked whether or not they were receiving antidepressant medication. The results are presented in Table 2.

Table 2. Hypothetical Results of a Case-Control Study of Patients With and Without Sexual Dysfunction

	Had Sexual Dysfunction	Did Not Have Sexual Dysfunction	Total
On treatment with antidepressant	8	32	40
Not on treatment with antidepressant	3	33	36
Total	11	65	76

Now, it is possible that only a few patients were prescribed antidepressants, and that the outpatient department was crowded with those who experienced antidepressant adverse effects such as sexual dysfunction. It is also possible that a lot of patients were prescribed antidepressants, that very few patients experienced adverse effects of any kind, and that the patients were doing well and so stayed away. Therefore, without knowing how many people in total were actually prescribed antidepressants, there is no way of calculating the absolute risk of antidepressant-related sexual dysfunction. Hence, there is no way of calculating the RR using the data in Table 2. However, the OR can be calculated and, because the data are exactly the same as in Table 1, the calculations and the result are also exactly the same. That is, the OR = 8:32/3:33, or 2.75.

ORs are also obtained in logistic regression analyses in which the value of the crude or univariate OR for a risk variable is adjusted for the presence of measured confounders. The adjusted OR presents a more accurate picture of the unique contribution of the risk variable to the outcome of interest.

The Importance of Absolute Risk

The RR and the OR should always be examined in the context of the absolute risk. For example, in a case-control study, Louik et al[12] found that the use of sertraline during pregnancy substantially increased the risk of omphalocele (OR = 5.7; 95% CI, 1.6–20.7). Omphalocele is rare in the population, and so, in this situation, the OR and the RR would probably be similar. If the risk of omphalocele in the general population is 0.02%,[13] the 5-fold increased risk with sertraline would result in an incidence of 0.1%. At the individual patient level, 0.1% is an almost negligible risk. Therefore, when the absolute risk is low, even a large increase in the RR or OR may not be clinically significant.

In contrast with the example explained above, if the absolute risk is high, then even a small increase in the RR or OR could be clinically important. For example, if the absolute risk of a condition is 30% in the reference population, then an RR of 1.2 means that this risk will increase by 20% after exposure to the risk factor. As 20% of 30 is 6%, the absolute risk will rise from 30% to 36% in patients exposed to the risk factor. A 6% increase in the absolute risk could be of concern.

In a nutshell, doubling of risk is of little clinical importance when the absolute risk is low; thus, for an individual patient, an increase in risk from 0.01% to 0.02% is negligible. However, doubling of risk is quite serious when the absolute risk is high, as in an increase in risk from 20% to 40%. Similar considerations apply to, for example, halving of risk.

Clinicians should therefore consider the absolute risk, draw upon their knowledge of the field, consider the clinical importance of the event, and exercise their judgment when

interpreting the importance of an RR or an OR when they manage the individual patient.

The Importance of Time

Risk is spread across time, and a treatment that doubles the "risk" of 2-year cancer survival could be more desirable than one that doubles the 2-month "risk" of cancer survival. RRs and ORs should therefore be interpreted in the context of time as well as absolute risk.

Parting Note

The risk of an illness is the chance, or the likelihood, that a person will develop that illness. A conditional risk, in contrast, is the chance, or the likelihood, that a person who fulfills some condition will develop an illness. For example, the lifetime risk of schizophrenia is about 1% in the general population; the conditional risk of the disorder in a boy may be 30%–40% if both of his parents have the disorder.[1]

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