This paper documents interesting and important findings from post-mortem brains of individuals with psychiatric diagnoses who committed suicide, and a variety of control groups.

Important findings include:
1. Decreased [3H]DAMGO across the CNS in people with schizophrenia who committed suicide, compared to controls as well as people with schizophrenia who died of non-suicide (latter two not different from each other)
2. Aging related decreases of endogenous opioid ligands wherein increases in the number of opioid binding sites are not matched by changes in levels of opioid (OPRM) protein which remains unchanged as a function of age.

MAJOR COMPULSARY REVISIONS

1. The many groups that are being compared make the paper a confusing read in its current state. Significant revision of the writing style is required to make the manuscript more comprehensible. Two very simple but huge improvements would be to simply organize the subjects into groups such as the “schizophrenia_suicide group”, “schizophrenia_non_suicide group” etc. and state the main point but tabulate the data instead of including it all in the text.

So for example, from the results section:
Our data showed the variance in [3H]DAMGO binding between people who had or had not died by suicide (F7,114 = 4.16, p=0.0004) was due to a 34% increase in radioligand binding in people with BP who had not died by suicide (Mean ± SEM; BP = 50.51±1.98, control = 37.63±1.83, p<0.05) and a 33 % decrease in radioligand binding in tissue from people with schizophrenia who died as a result of suicide (Mean ± SEM; schizophrenia (suicide) = 25.31±3.17, control = 37.63±1.83, p<0.05; Figure 1c).

Could be rewritten as:
Changes in [3H]DAMGO binding as a function of suicide were due to 34% increase in binding in BP_non_suicide group and a 33% decrease in binding in the schizophrenia_suicide group (Table X, Figure 1c).

2. The very large variability of sizes of the groups being compared is worrying.
BP_NON_SUICIDE = 8
BP_SUICIDE = 5
SCHIZOPHRENIA_NON_SUICIDE = 26
SCHIZOPHRENIA_SUICIDE = 12
MDD_NON_SUICIDE = 5
MDD_SUICIDE = 15
SUICIDE_NO_DISORDER = 9
CONTROLS = 51

It is unclear if these comparisons are statistically sound. The demographics of the samples are also quite variable. While the authors try to control for these factors by including demographic characteristics that were significantly different (such as age and ph) as covariates in their analyses and note if the main effects still remain, it is unclear as to how much variability in the data is accounted for by the co-variate alone.

For instance, people in the schizophrenia_suicide group were significantly younger than controls (as well as non_suicide_schizophrenia group, MDD and BP groups)

The schizophrenia_suicide group showed a 33% decrease in OPRM binding in the BA24 compared to controls

As the authors note, [3H]DAMGO binding increases with age (younger age of schizophrenia_suicide_group could account for lower binding), and age was a significant covariate in their analyses – (although covariate X predictor interactions were not reported)

Perhaps one way of alleviating doubts would be to do a component analysis that reports how much of the variance in the data was accounted for by age and how much was accounted for by psychiatric_diagnosis_suicide status.

3. Only comparisons of the schizophrenia_suicide group with the control group are reported and not comparisons of schizophrenia_suicide with schizophrenia_non_suicide. If suicidality is a main focus of the paper, isn’t that the most interesting comparison?

4. Another issue is length of exposure to antipsychotic/psychotropic medication (lesser in people who died as a result of suicide at a young age, for instance) which is likely to affect the endogenous opioid system. Further, the different systems targeted by different drugs (eg. opioid agonists versus SSRIs) also have the potential for impacting OPRM binding. This might not be something the authors can control for given the constraints of the sample – but should remain an important consideration in this work.

OVERALL: this paper presents potentially valuable insight into the interaction of the opioid system with suicidality. With significant revisions to the writing style
and a thorough revisitation of the statistics presented here to make them both more informative, as well as more pliable to the reader (a hard task indeed!), it would make a good contribution to the current literature.

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Not suitable for publication unless extensively edited

**Statistical review:** Yes, but I do not feel adequately qualified to assess the statistics.

**Declaration of competing interests:**

I declare that I have no competing interests