LAMPIRAN

Lampiran 1. Naskah publikasi yang di*submit*

Effectiveness of Anticonvulsants Compared to Antidepressants in Reducing Pain in Diabetic Neuropathy Complications

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ABSTRACT

Diabetes mellitus is a non-communicable disease which is a global challenge. Diabetes that is chronic and uncontrolled can cause various complications, one of which is diabetic neuropathy. One of the most common complications is neuropathy pain or painful diabetic peripheral neuropathy (DPN), at least 25% - 30% of people with diabetes mellitus experience diabetic neuropathy pain. Diabetic neuropathy pain can interfere with work or daily activities, so treatment is necessary. Through this literature review, we will conduct an assessment of effective pharmacological therapy in reducing or alleviating diabetic neuropathy pain. The classes of drugs under review are anticonvulsants (carbamazepine, gabapentin, and pregabalin) and antidepressants (amitriptyline and duloxetine). This type of literature review is narrative review, the database used to search for literature sources, namely, PubMed, PMC, and Google Scholar uses keywords, the search results are limited to articles published between 2012 and 2022, free full text using Indonesian or Indonesian. English. Based on a review of the literature, the pregabalin group had the best efficacy, and the number of evidence-based medicines used pregabalin, followed by duloxetine, amitriptyline, and gabapentin. The most common side effects found in all types of drugs reviewed were dizziness, headache, nausea, and

vomiting. However, it should be noted that in some groups there was decreased consciousness or somnolence, constipation, and anorexia.
Keywords: Anticonvulsant, Antidepressant, Painful Diabetic Neuropathy

INTRODUCTION

Diabetes mellitus is a non-communicable disease which is a global challenge, according to the World Health Organization (WHO) 2020 diabetes mellitus is included in the top ten diseases that cause the most deaths each year [(27)]. In 2015, there were 5 million deaths from diabetes, Indonesia ranked seventh in the world with cases of diabetes in adults, namely 10 million people. Diabetes that is prolonged or chronic and uncontrolled can cause various complications, one of it, which is called diabetic neuropathy.[1]

One of the most common complications is neuropathy pain or painful diabetic peripheral neuropathy (DPN), at least 25% - 30% people with diabetes mellitus experience diabetic neuropathy pain.[2] Some of the symptoms of DPN are numbness, tingling, stabbing pain, burning sensation, electric shock sensation, pain in the lower limbs and/or hands or often referred to as "glove-stocking".[3] Diabetic neuropathy pain can interfere with work or daily activities, so treatment is necessary.[4]

Therefore, through this literature review, we will conduct an assessment of how effective pharmacological therapy in reducing or alleviating diabetic neuropathy pain. The classes of drugs being studied are anticonvulsants (carbamazepine, gabapentin, and pregabalin) and antidepressants (amitriptyline and duloxetine). when prescribing these drugs.

METHOD

The preparation of this literature review was carried out by collecting and reviewing literature from various valid sources, the database used to search for literature sources are PubMed, PMC, and Google Scholar. The purpose of this literature review was to compare the efficacy of anticonvulsants and antidepressants in reducing diabetic neuropathy pain.

RESULT AND DISCUSSION

Recommendations for Diabetic Neuropathy Pain Pharmacology

Pharmacological therapy recommendations from various guidelines such as the American Diabetes Association (ADA), Neuropathic Pain Special Interest Group of the International Association for the Study of Pain (NeuPSIG IASP), the National Institute for Health and Care Excellence (NICE), and the European Federation of Neurological Societies (EFNS), recommended duloxetine, gabapentin, pregabalin, tricyclic antidepressants such as amitriptyline for the treatment of diabetic neuropathy pain.[5] In Indonesia, based on the Decree of the

Minister of Health of the Republic of Indonesia in 2020, the use of amitriptyline, duloxetine gabapentin, and pregabalin are recommended for pharmacological treatment of diabetic neuropathy pain.[6]

Anticonvulsant Effectiveness Compared With Antidepressants

Pharmacological management of diabetic patients with neuropathy complications to reduce pain, from twelve literature studies reviewed using antidepressants and anticonvulsants, the following are the results of a literature review.

Amitriptyline

Amitiptyline is a drug with high efficacy in the antidepressant class, amitriptyline is a tricyclic antidepressant drug (TCA), the way TCA works is by inhibiting serotonin and noradrenaline. In addition, TCA blocks NMDA receptors in the spinal cord can cause central sensitization.[7]

In terms of efficacy, when it compared with pregabalin, based on a study by Sankar *et al*., both drugs have a good effect on reducing pain, but statistically amitriptyline is more significant.[8] In studies that compared the effectiveness of amitriptyline, duloxetine, and pregabalin, all types of drugs were effective, but there were no significant differences.[9]

In terms of the number of adverse events, several studies have shown that amitriptyline has fewer AEs than pregabalin.[9,10] However, there are studies showing that the incidence of AE is more prevalent in the amitriptyline group.[11,12]

Carbamazepine

Carbamazepine belongs to the anticonvulsant class of drugs, one of how it works is to affect the nerve fibers that produce pain feeling, and that is by suppressing Aδ and C fibers. Decrease conduction in sodium and potassium, as well as suppression of spontaneous peripheral ectopic activity is thought to have a role in reducing diabetic neuropathy pain.[13]

A study conducted by Rahman *et al*., by comparing the pain-reducing effect of diabetic neuropathy between groups Bangladesh given carbamazepine and amitriptyline. There were a total of 110 people, 54 people belong to the amitriptyline group, and 56 people belong to the carbamazepine group. During the study period, 2 persons from the carbamazepine group and 4 persons from the amitriptyline group were excluded from the study due to having non-follow-up. Then, there were 2 people from carbamazpine group who developed skin rashes, so they could not continue the study. Nonetheless, the result showed that carbamazepine showed significant pain relief compared to amitriptyline.[14]

Another study conducted by Saeed *et al*., showed that carbamazepine was successful in reducing pain severity by 30% at each follow-up, differing in mean standard deviation from 5.8±2.0 to 3.6±2.2 at the end of the study. However,

carbamazepine did not provide a significant pain reduction effect when compared to pregabalin based on a study conducted by Razazian *et al.*[15,16]

Duloxetine

Duloxetine is an SNRI drug, that works by inhibiting serotonin-norepinephrine reuptake, inhibition of these neurotransmitters results in reduced pain transmission signals from the periphery to the central nervous system, this is because serotonin and norepinephrine are neurotransmitters that are responsible for giving pain signals.[17]

Duloxetine works effectively in reducing pain, when compared with pregabalin and amitriptyline there is no significant difference in reducing pain.[9] However, when compared with pregabalin or gabapentin, duloxetine showed significantly more efficacy than the two anticonvulsant drugs[18] and duloxetine is better tolerated.[9,19] Research by Tesfaye *et al*., tried to combine duloxetine and pregabalin and then compared it with duloxetine and pregabalin monotherapy, the results of the combination of the two drugs were effective but not more significant than monotherapy.[20]

Gabapentin

Gabapentinoids are a class of drugs derived from gamma-aminobutyric acid (GABA) neurotransmitter inhibitors. There are several drugs from the gabapentinoid class, one of which is gabapentin. Gabapentinoids affect the number of calcium channels in the plasma membrane. In the voltage-gated calcium channels, the area of the central nervous system binding occurred with the alpha-2/delta-1 sub-unit resulting in complex macromolecular destabilization on the presynaptic surface, this is the mode of action of gabapentinoids.[7]

In comparison with antidepressants, based on research by Majdinasab *et al.*, when it compared with duloxetine, gabapentin showed a faster pain reduction effect than duloxetine. However, the side effects were more commonly found and have lower tolerability in the pregabalin group. Nonetheless, both drugs were effective in reducing pain, and there was no significant difference. Research conducted in Indonesia, when comparing amitriptyline, gabapentin, and pregabalin, found no significant differences in analgesic effects.[10]

Apart from antidepressants, several studies have compared the efficacy of gabapentin with other drugs in the same class, namely pregabalin. One study by Alvarado and Navarro used gabapentin combined with B complex vitamins (B1/B2) to be compared with pregabalin. Both drugs were effective in reducing pain by 78% in the pregabalin and vitamin B combination group and 85% in the pregabalin group, but there was no significant difference between the two drugs. ($p = 0.1333$).[11] Research using placebo has also been conducted by Pandey *et al*., there is no statistically significant difference.[21]

Gabapentin is effective in reducing diabetic neuropathy pain, this is proven through research conducted in Indonesia by Zhulhajsyirah *et al*., the statistical value of pain reduction is p-value <0.05, there is an average decrease in pain scale as measured using the *Numeric Pain Rating Scale* (NPRS) from 3.28 to 1.14.[22]

Pregabalin

Gabapentinoids are a class of drugs derived from the inhibitory neurotransmitter gamma-aminobutyric acid (GABA). There are several drugs from the gabapentinoid class, one of which is pregabalin. Gabapentinoids that affect the number of calcium channels present in the plasma membrane. In the voltage-gated calcium channels in the area of the central nervous system binding occurs with the alpha-2/delta-1 subunit resulting in complex macromolecular destabilization on the presynaptic surface, this is the mode of action of gabapentinoids.[7] What distinguishes pregabalin from gabapentin is the potential for a higher ratio of binding to alpha-2/delta-1 which has a higher affinity.[17]

Pregabalin is an anticonvulsant which is a first-line drug in reducing diabetic neuropathy pain, this drug is often used for research on diabetic neuropathy pain medication. In research, there has been a lot of evidence based medicine which shows that pregabalin is effective. However, it is not uncommon to find that pregabalin has the same efficacy values as gabapentin, amitriptyline, and duloxetine.

Pregabalin is effective in significantly reducing neuropathic pain in diabetes mellitus type 1 and type 2.[23] In comparison with amitriptyline, one study showed that pregabalin was superior in providing a pain reduction effect, namely as much as 65% of the pregabalin group compared to amitriptyline, namely 47.5% of the group given amitriptyline.[24] In the same group, when compared with carbamazepine it is more significant in reducing pain.[15]

Judged based on the number of adverse events, there are two studies showing that pregabalin was found to have fewer adverse events than duloxetine and amitriptyline.[12,25]

Tesfaye *et al*., conducted a study using a combination of duloxetine and pregabalin, the results were effective but not more significant than monotherapy of each drug.[20] The Chinese placebo study, however, showed no statistically significant improvement, but was effective in this subpopulation, and pregabalin was well tolerated.[26]

Side Effects

Side effects are one of the determinants in considering the choice of medication given, the following are the side effects found based on the results of a literature review.

Amitriptyline

Amitriptyline is one of the antidepressant groups that is often used to reduce diabetic neuropathy pain, the side effects that can occur are very diverse. Some of the side effects that may occur are dizziness, somnolence, dry mouth, fatigue, constipation, postural hypotension, drowsiness or drowsiness, nausea, difficulty urinating, daytime sleepiness, increased sleep duration, and flu-like symptoms.[8,10,12,14,24] The results of the review of the number of percentages and side effects can be seen in (Figure 1).

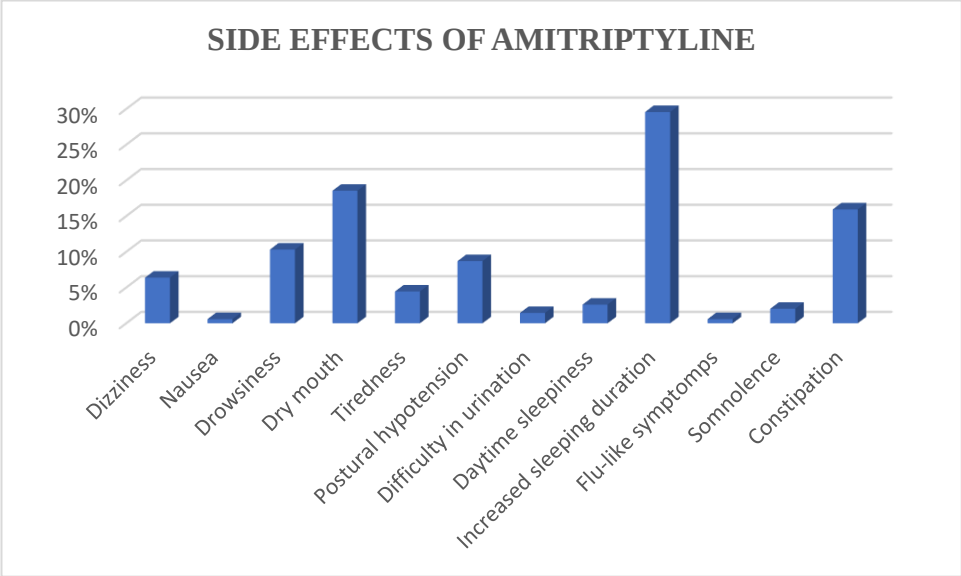

Figure 1. Side effects of amitriptyline that were found in literature review.[8,10,12,14,24]

Carbamazepine

In its class, carbamazepine is a drug with lower efficacy compared to pregabalin and gabapentin in reducing diabetic neuropathy pain. However, the adverse events (AE) that often occur are mild. Some of the side effects that often occur are drowsiness, dizziness, nausea, and headaches. In addition, some of the side effects found were somnolence, impotence, bulimia, dyspepsia, asthenia, and unsteadiness.[14–16] The results of the review of the number of percentages and side effects can be seen in (Figure 2).

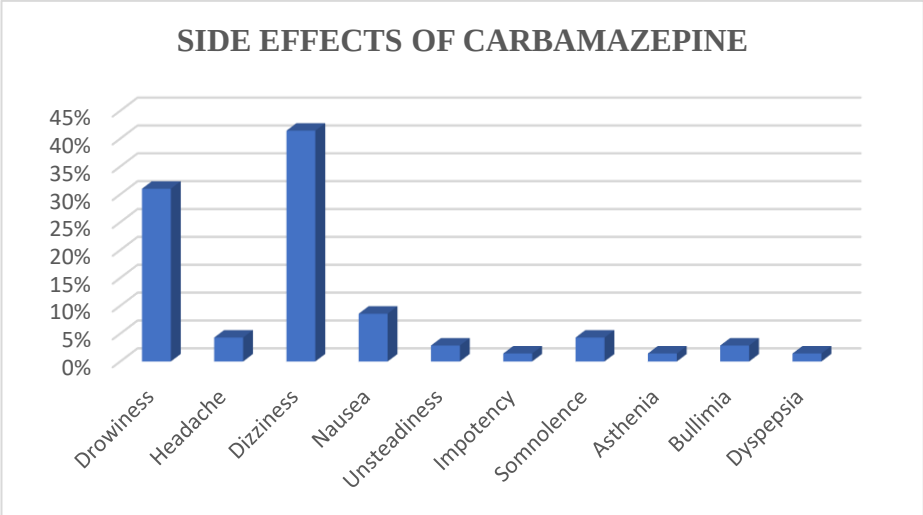

Figure 2. Side effects of carbamazepine that were found in literature review.[14–16]

Duloxetine

This class of antidepressant drugs is often used to reduce diabetic neuropathy pain. Side effects that often occur are somnolence, nausea, vomiting, headaches, and dizziness. In addition, side effects that can occur are anorexia, diarrhea, chills, agitation, tremor, muscle rigidity, hyperthermia, stomach cramps, cold sweats, constipation, blurred vision, orthostatic hypotension, and blurred vision.[25,27] The results of the review of the number of percentages and side effects can be seen in (Figure 3).

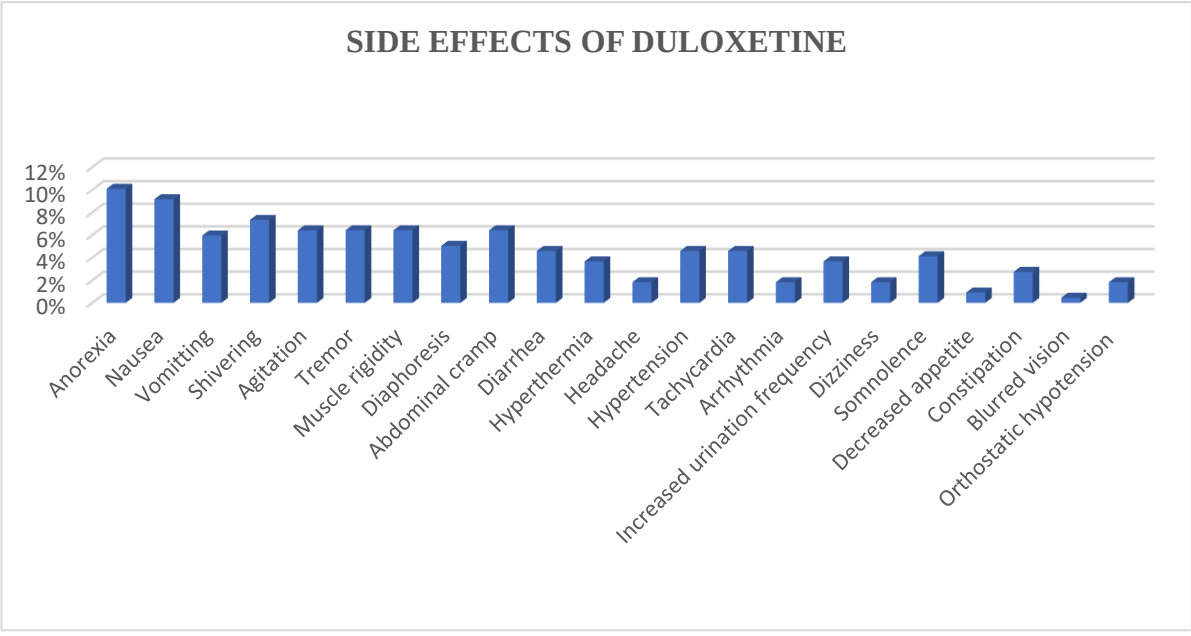

Figure 3. Side effects of duloxetine that were found in a literature review.[25,27]

Gabapentin

Gabapentin is a first-line drug in the treatment of diabetic neuropathy pain, its level of efficacy is not much different from pregabalin as a first-line anticonvulsant class. The most common side effects are dizziness, drowsiness, and headaches. Some other side effects that can occur are ataxia, somnolence, edema, confusion, vertigo, and drowsiness.[10,11,22]

Pregabalin

In reducing diabetic neuropathy pain, pregabalin is a drug that is often used, especially in research as a comparison, besides that pregabalin is included as the first line in the treatment of diabetic neuropathy pain.

There are quite a number of studies using pregabalin and the side effects have been found to affect various organ systems such as the cardiovascular, nerve system, endocrine, and metabolic systems. Side effects found based on studies using pregabalin are dizziness, nausea, headache, drowsiness, vertigo, somnolence, vomiting, anorexia, confusion, edema, fatigue, weight changes, hypertension, constipation, tachycardia, diarrhea, daytime sleepiness, flu-like symptoms, increased sleep duration, increased urination, impotence, asthenia, dyspepsia, decreased appetite, sexual dysfunction, hypoglycemia, and arthralgia.[8,10,12,15,23–25,27] The results of the review of the number of percentages and side effects can be seen in (Figure 4).

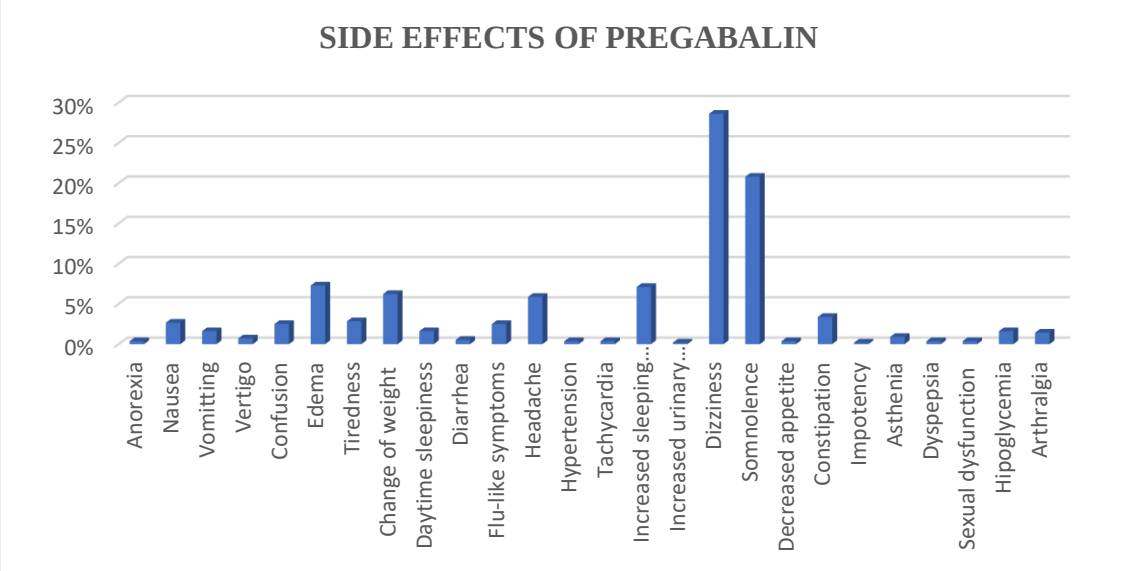

Figure 4. Side effects of pregabalin that were found in a literature review.[8,10,12,15,23–25,27]

CONCLUSION

The results of the literature review showed that the use of the drug pregabalin was most often used in research, both as a comparison and to measure

the efficacy of pregabalin. From all studies, it can be concluded that pregabalin has better efficacy and more evidence based medicine. Nonetheless, amitriptyline, duloxetine, and gabapentin also showed good efficacy results, but there were no significant differences. Another comparator, carbamazepine, is one of the drugs reviewed in this literature review, although carbamazepine is more often indicated for the treatment of epilepsy and has not been recommended for use in diabetic neuropathy pain, however, there are several studies showing that carbamazepine is effective in reducing diabetic neuropathy pain. However, further research and studies should be carried out for carbamazepine, because for now there is still little research and literature using carbamazepine as a pain reliever for diabetic neuropathy.

In terms of side effects, the most universal symptoms that are present in all drugs are dizziness, headache, nausea, and vomiting. It should be noted that several types of drugs such as amitriptyline, carbamazepine, duloxetine, and pregabalin have somnolent side effects.

DISCLOSURE

There was no conflict of interest related to this review.

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AUTHOR CONTRIBUTIONS

AMAN participated in manuscript writing, collected data and article to review. LI, NT, and NDI revising and proofreading for the final manuscript.

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Lampiran 2. Bukti *submit* jurnal

Dear editor of The Borneo Review of Medical Sciences
To whom it may concern
I submitted my article entitle:
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for your journal. Please consider it for publication.
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Corresponding author

Effectiveness of Anticonvulsants Compared to Antidepressants in Reducing Pain in Diabetic Neuropathy Complications

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Lampiran 3. *Letter of Acceptance* (LoA)

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Dear Alifia Mazaya Aliya Nugroho, Laily Irfana, Nenny Triastuti, Nina Devi Indrawati

I am pleased to inform you that your manuscript titled as " Effectiveness of Anticonvulsants Compared to Antidepressants in Reducing Pain in Diabetic Neuropathy Complications " (Manuscript Number: BRMS/2023-01-002 was accepted for publication in the Borneo Review of Medical Sciences

You may download the file.

I would like to remind that you could send your future manuscripts to the Borneo Review of Medical Sciences (BRMS)

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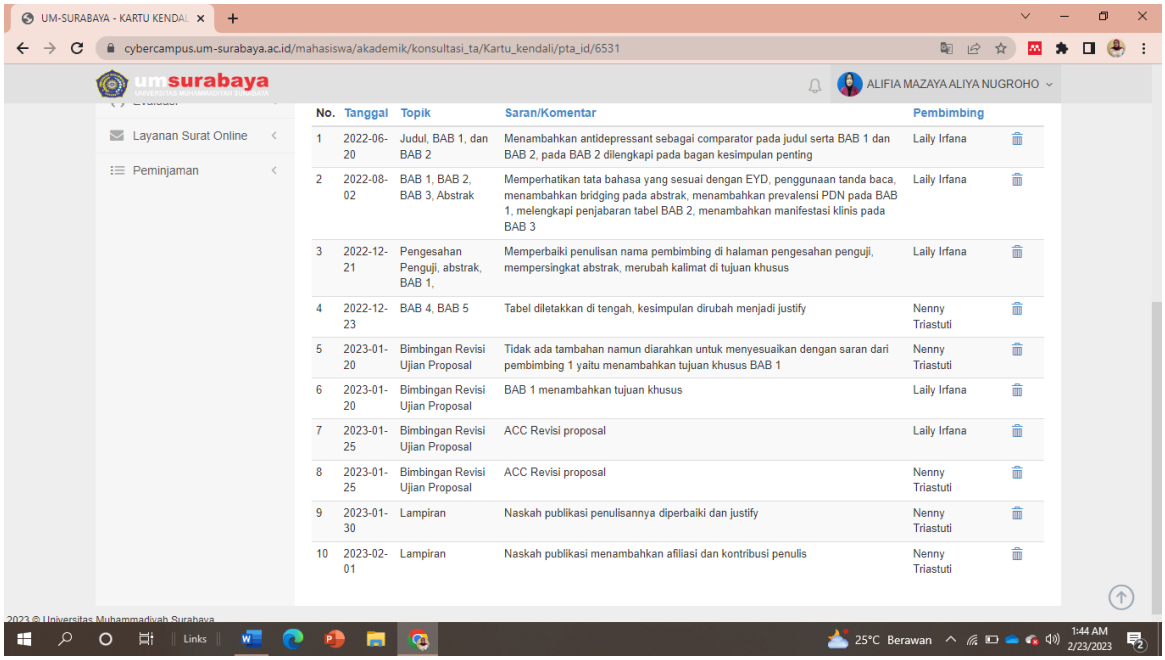
Lampiran 4. Bukti bimbingan *cybercampus*



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ALIFIA MAZAYA ALIYA NUGROHO

Layanan Surat Online

Peminjaman

No.	Tanggal	Topik	Saran/Komentar	Pembimbing
1	2022-06-20	Judul, BAB 1, dan BAB 2	Menambahkan antidepressant sebagai comparator pada judul serta BAB 1 dan BAB 2, pada BAB 2 dilengkapi pada bagan kesimpulan penting	Laily Irfana
2	2022-08-02	BAB 1, BAB 2, BAB 3, Abstrak	Memperhatikan tata bahasa yang sesuai dengan EYD, penggunaan tanda baca, menambahkan bridging pada abstrak, menambahkan prevalensi PDN pada BAB 1, melengkapi penjabaran tabel BAB 2, menambahkan manifestasi klinis pada BAB 3	Laily Irfana
3	2022-12-21	Pengesahan Penguji, abstrak, BAB 1,	Memperbaiki penulisan nama pembimbing di halaman pengesahan penguji, mempersingkat abstrak, merubah kalimat di tujuan khusus	Laily Irfana
4	2022-12-23	BAB 4, BAB 5	Tabel diletakkan di tengah, kesimpulan dirubah menjadi justify	Nenny Triastuti
5	2023-01-20	Bimbingan Revisi Ujian Proposal	Tidak ada tambahan namun diarahkan untuk menyesuaikan dengan saran dari pembimbing 1 yaitu menambahkan tujuan khusus BAB 1	Nenny Triastuti
6	2023-01-20	Bimbingan Revisi Ujian Proposal	BAB 1 menambahkan tujuan khusus	Laily Irfana
7	2023-01-25	Bimbingan Revisi Ujian Proposal	ACC Revisi proposal	Laily Irfana
8	2023-01-25	Bimbingan Revisi Ujian Proposal	ACC Revisi proposal	Nenny Triastuti
9	2023-01-30	Lampiran	Naskah publikasi penulisannya diperbaiki dan justify	Nenny Triastuti
10	2023-02-01	Lampiran	Naskah publikasi menambahkan afiliasi dan kontribusi penulis	Nenny Triastuti

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Lampiran 5. Pernyataan Persetujuan Publikasi Tugas Akhir untuk Kepentingan Publikasi

PERNYATAAN PERSETUJUAN PUBLIKASI

TUGAS AKHIR UNTUK KEPENTINGAN AKADEMIS

Sebagai civitas akademika Universitas Muhammadiyah Surabaya (UMSurabaya), saya yang bertandatangan di bawah ini:

Nama : Alifia Mazaya Aliya Nugroho

NIM : 20191880052

Fakultas : Kedokteran

Program Studi : S1 Pendidikan Dokter

Demi pengembangan ilmu pengetahuan, menyetujui untuk memberikan kepada Program Studi Pendidikan Dokter Fakultas Kedokteran UMSurabaya Hak Bebas Royalti Non-Eksklusif atas karya ilmiah saya yang berjudul **"EFEKTIVITAS ANTIKONVULSAN DIBANDINGKAN DENGAN ANTIDEPRESAN DALAM MENURUNKAN NYERI PADA KOMPLIKASI NEUROPATI DIABETIK"** beserta perangkat yang ada (jika diperlukan).

Dengan hak bebas royalti non-eksklusif ini, Program Studi Pendidikan Dokter Fakultas Kedokteran UMSurabaya berhak menyimpan, mengalih media/formatkan, mengelola dalam bentuk pangkalan data (*database)*, merawat dan mempublikasikan tugas akhir saya selama tetap mencantumkan nama saya dan atau pembimbing saya sebagai penulis dan pemilik Hak Cipta.

Demikian pernyataan ini saya buat dengan sebenar-benarnya.

Surabaya, 14 Juli 2023

Yang membuat pernyataan,

ALIFIA MAZAYA ALIYA NUGROHO