WHITE PAPER
SUMMARY OF RECOMMENDATIONS FOR THE PREVENTION AND TREATMENT OF RLS/WED AUGMENTATION
A COMBINED TASK FORCE OF THE IRLSSG, EURLSSG AND THE RLS-FOUNDATION

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1. PREAMBLE

Dopaminergic drugs have been widely used over the last decades for the treatment of restless legs syndrome (RLS)/Willis-Ekbom disease (WED). Although most patients initially respond well and this class of drugs is generally well tolerated, treatment efficacy diminishes in many patients over the course of time.[1] Moreover, dopaminergic drugs can specifically worsen overall disease severity through a process called augmentation.

For these reasons an evolving or lack of response to dopaminergic treatment of RLS/WED represents a common problem and challenge in daily practice. There are currently no augmentation treatment guidelines which primary care physicians and non-expert specialists can use. For this reason, the IRLSSG decided to create a Task Force together with the EURLSSG (European RLS Study Group, www.eurlssg.org) and the WED Foundation (www.willis-ekbom.org) to reach a consensus on the prevention and treatment of RLS/WED augmentation.

2. IDENTIFICATION OF RLS/WED AUGMENTATION

Augmentation is the main long-term complication of dopaminergic drugs and one of the main reasons for loss of response to dopaminergic treatment in RLS/WED. Augmentation is a treatment-related increase in RLS/WED symptoms that emerges with the long-term dopaminergic treatment of RLS/WED. This condition was first described in 1996 when it was reported in 73% of RLS/WED patients treated with levodopa, and was severe enough to require a change of treatment in 50% of patients.[2] Although augmentation was originally attributed to long-term treatment with levodopa, since 1996 it has become evident that it also develops during long-term treatment with any of the approved dopamine agonists:[1] a recent US community-based study estimated that 76% of all patients treated with levodopa or a dopamine agonist showed indications for augmentation, with a yearly incidence of 8%.[3]

Comparison of augmentation rates between different classes of dopaminergic medications is difficult because of differing metrics used and the absence of comparative studies. However, it is accepted that augmentation is highest with levodopa,[4] which has a different mechanism of action, metabolism and a much shorter half-life than the commonly used dopamine agonists. There is some, but not definite evidence, that long-acting dopaminergic agents cause less augmentation than intermediate/short-acting dopaminergic agents.[5, 6]

The current definitions of augmentation include the original definition described by Allen and Earley in 1996,[2] the 2003 National Institute of Health (NIH) criteria [7] and the 2006 Max Planck Institute (MPI) criteria.[8] These criteria highlight the time advance of symptoms (2-4 hours), a shorter latency of symptoms at rest, a spread of symptoms proximally in the legs and to the arms, a shorter duration of efficacy, and/or a greater intensity of symptoms.

There are no validated screening tools for augmentation, and although several research criteria for RLS/WED augmentation have been published,[2, 7, 8] these are often impractical in clinical practice; in particular it is difficult for patients to quantify their symptoms, to remember the time of symptom onset prior to medication initiation, or to specify the exact frequency that symptoms are worse in a week. These criteria also include a paradoxical response to treatment whereby symptoms improve a few weeks after drug dose is decreased and may worsen after a few weeks, or even years, when the drug is increased. However, in clinical practice the drug dose is usually not increased until augmentation has been already diagnosed, and conversely with dose decrease most patients' symptoms do not improve for several days to weeks due to withdrawal symptoms. Moreover, increasing doses of dopaminergic agents, especially if taken earlier before RLS/WED onset, often improves symptoms, only for them to become worse again after a while on the higher dose.

To facilitate the identification of augmentation in clinical practice, physicians might wish to consider that augmentation is likely whenever a patient who has been on stable treatment for six months requests more medication. The IRLSSG task force recommends four

screening questions, that have yet to be validated, that may be used in clinical practice in patients currently under treatment with dopaminergic agents. An affirmative answer to any of these four questions should lead the physician to consider that augmentation is present:

1. Do RLS/WED symptoms appear earlier than when the drug was first started?
2. Are higher doses of the drug now needed to control the RLS/WED symptoms compared to the original effective dose?
3. Has the intensity of symptoms worsened since starting the medication?
4. Have symptoms spread to other parts of the body (e.g., arms) since starting the medication?

It is important to remember that augmentation may progress in a fluctuating manner over time and needs to be distinguished from natural progression or fluctuations in the severity of RLS/WED. Similarly, the worsening of RLS/WED symptoms due to other identifiable factors also needs to be considered. These factors include iron deficiency, exacerbating medications such as anti-histamines, dopamine-receptor blockers or serotonergic antidepressants, poor medication compliance, sleep deprivation, lifestyle changes (e.g., changes in mobility), appearance of other physiological or pathological conditions known to trigger or exacerbate RLS/WED (pregnancy, renal insufficiency, other sleep disorders particularly sleep-disordered breathing.).

3. PREVENTING AUGMENTATION

Some degree of augmentation has been reported with the use of all investigated dopaminergic drugs as well as for the atypical opioid tramadol[9] In the virtual absence of direct comparative studies for augmentation rates with different dopaminergic medications, the incidence rate seems highest during treatment with levodopa[2] and is higher for shorter-acting (pramipexole, ropinirole)[10-12] than longer-acting dopamine agonists (cabergoline, rotigotine).[5] However, as mentioned above, such evidence is far from definite. Furthermore, it is unclear whether this finding is related to masking of earlier

symptom onset by the longer-acting dopaminergic agents or if it is truly an augmentation-sparing effect.

Nevertheless, there is consensus that the greatest risk factor for augmentation is treatment with dopaminergic agents or is even exclusively related to the specific action of the dopaminergic system, and the risk of developing augmentation is strongly correlated to the dose and duration of dopaminergic usage.[1, 3, 11, 13]

Therefore, the most effective preventive strategy involves reducing the dopaminergic load by using the lowest effective dose.

Other factors that are thought to contribute to an increased risk of augmentation include low iron stores,[14, 15] greater severity of RLS/WED symptoms prior to initiation of treatment,[2, 3] and possibly a family history of RLS or lack of neuropathy.[16]

a) First-line treatment of de novo patients

Since RLS is usually a chronic condition requiring treatment for many years, the choice of the initial treatment needs to consider the long as well as the short term effects of the drug. Many patients on dopaminergic treatment will have a gradual and insidious development of augmentation. Since augmentation is similar to natural progression of the disease it can be difficult to detect before it becomes a significant problem. The physician, particularly if not very experienced in long-term management of RLS, should keep dopaminergic load as low as possible in previously untreated RLS/WED patients and consider using for initial RLS treatment medications that, while effective, have little or no risk of augmentation.

The physician should consider a therapeutic trial with alpha-2-delta ligands (i.e. gabapentin, gabapentin enacarbil, pregabalin), as these are alternative, effective first-line treatment for RLS without risk of augmentation. However, their short and intermediate term side effects should also be a factor in consideration when selecting the most appropriate initial

treatment.

.. The risk of augmentation has to be weighed against the risks and benefits associated with each treatment, the patient's response to previous treatment for RLS/WED, possible interaction with other treatments, and the patient's comorbid conditions and clinical status. For instance, dopamine- agonists may be preferable to $\alpha_2\delta$ calcium-channel ligands as first-line treatment in patients with excessive weight, severe depression of suicidal ideation or cognitive impairment, and possibly associated with clinically problematic periodic limb movements. Furthermore, given that the highest rates of augmentation are found with levodopa, the use of levodopa for the daily treatment of RLS/WED should be avoided, at least for long-term chronic treatment.

In addition, the use of non-dopaminergic options as a first-line treatment is limited by the fact that in some regions of the world (i.e., Europe) no such treatments are approved for RLS/WED.

b) Adjusting daily treatment of RLS/WED to prevent augmentation

If a patient is already being treated with a dopaminergic agent, the lowest possible cumulative daily dopaminergic dose should be used to control the majority of bothersome RLS/WED symptoms, and the total daily dose should not exceed maximum recommended levels. Physicians should explain to patients that the goal of treatment is not to completely eradicate symptoms but to ensure they do not interfere with quality of life, and that if symptoms become bothersome the dose can be increased once, in agreement with the physician, but that this will increase the risk of developing augmentation. A non-dopaminergic agent can be added if concerns about dosing of the dopaminergic drug occur. These therapeutic decisions should also be based on other factors related to patient characteristics such as age, previous episodes of augmentation and vulnerability to class-related side effects.

c) Intermittent (non-daily) treatment of RLS/WED to prevent augmentation

The daily treatment of RLS/WED should be deferred as long as possible until symptoms occur almost daily. However, a number of factors make this goal difficult to achieve. First, in patients with intermittent RLS/WED the emergence of symptoms is often unpredictable. Second, many patients find that it is more effective to take medication prior to onset of symptoms, preventing their occurrence, rather than waiting until after symptom onset. Nevertheless, the goal of intermittent dosing should be pursued, especially in presence of a rare occurrence of symptoms (<1-2/week) or as preventive medications before predictable conditions of immobility. Levodopa may be used for intermittent treatment at most two to three times a week, but should not be used for daily treatment given the high risk of augmentation with this medication.

d) Using longer acting dopamine agonists

As mentioned before, longer-acting dopaminergic agonists may cause less augmentation than shorter acting dopamine agonists. As with all other dopamine agonists the dose of longer acting dopamine agonists should not be increased above recommended levels for RLS/WED.

e) Dose reduction

Longitudinal studies demonstrate that RLS/WED symptom intensity fluctuates and that some patients even appear to go into spontaneous remission. Therefore, in patients with a history of notable fluctuating RLS/WED symptoms the clinician may consider it appropriate to intermittently attempt to reduce or even discontinue the dose in order to ensure that the patient is being treated with the lowest effective dose. If done so, the patient should be made aware that withdrawal symptoms may occur for several days or even weeks after dose reduction and this has to be distinguished from the requirement for continued medication treatment or a true worsening of RLS/WED symptoms.

f) Switching to an alternate dopaminergic agent

Switching from one dopamine agonist to another is generally not considered useful for preventing (or treating) augmentation, except for switching from levodopa or a short-acting

dopamine agonist to a long-acting formulation of a licensed dopamine agonist (e.g., transdermal rotigotine). Physicians may wish to consider long-acting formulations of dopamine agonists as an alternative to reduce the risk of augmentation although there is no evidence that this will ultimately delay or prevent augmentation.

RECOMMENDATION

- **Because many patients on dopaminergic treatment will develop augmentation, the physician, particularly if not very experienced in long-term management of RLS, should consider using for initial RLS treatment medications that, while effective, have little or no risk of augmentation.**
- **Alpha-2-delta ligands are effective first-line agents without the risk of augmentation but their profile of short- and intermediate- term side effects should be considered in selecting the most appropriate drug. Such recommendation is also limited by the fact that alpha-2-delta ligands are not approved in certain regions of the world (e.g., Europe).**
- **Patients with low iron stores should be given appropriate iron supplementation.**
- **If dopaminergic drugs are appropriate or needed, the daily dose should not exceed that recommended for RLS/WED treatment. Daily treatment with dopaminergic drugs should start only when symptoms have a significant impact on quality of life in terms of frequency and severity; intermittent treatment might be considered in intermediate cases.**

4. TREATMENT OF AUGMENTATION (Figure 1)

a) Elimination of exacerbating factors

The first step in treating augmentation consists in the elimination and/or correction of any exacerbating factors:

The patient's serum ferritin level should be measured, and, if the concentration is < 50-75 µg/mL, or if transferrin saturation is less than 20%, supplementation with orally administered iron is recommended unless poorly tolerated or contraindicated. Intravenous (IV) iron can also be considered.

It is important to ask the patient about any lifestyle changes (sleep deprivation, alcohol use, decreased mobility), or changes in medical factors (use of dopamine- antagonists, antihistamines or antidepressants, recent opioid discontinuation, blood loss), that can contribute to an earlier onset or an increase in the severity of RLS/WED symptoms.

Any extrinsic factors exacerbating RLS/WED expression should be adjusted as much as possible to reduce the need for RLS/WED medication changes.

b) Mild symptoms of augmentation

Augmentation exists along a continuum of severity and is arbitrarily considered mild if all of the following are present: symptoms manifest predominantly as a temporal shift of symptoms to earlier in the day compared to before starting treatment; dopaminergic monotherapy is at a total daily dose at or below maximum recommended levels; symptoms cause only mild distress; and there has been no prior increase in total dose above what was previously therapeutically effective.

In cases of mild augmentation the physician can choose one of two strategies based on the individual characteristics of the patient (see Figure 1):

i) Continue current dopamine agonist therapy

Continue treatment with the same dopamine agonist according to one of three possibilities:

- The first option consists of keeping the total dose the same, but either dividing it or advancing the time of the dose to before symptom onset.
- If dividing or advancing the dose fails, then an alternative is to increase the dose, usually the earlier rather than the nighttime dose. If, however, the augmentation

distress occurs mostly from symptoms breaking through at night then the nighttime dose could be increased. Make sure that the maximum recommended dose is not exceeded and that the patient is carefully monitored for continued augmentation. Only one total daily dose increase should be performed.

- If these dose adjustments fail, a switch to another medication is recommended.

ii) Complete switch

The physician may consider that the present augmentation, although not severely distressing, is a harbinger of more severe augmentation and that it is appropriate to switch drugs earlier rather than later. It must be considered that addressing the augmentation problem earlier may make the switch much easier and less stressful for the patient.

The patient can either be switched to:

- an α2δ calcium-channel ligand (pregabalin, gabapentin enacarbil),

or alternatively, depending on the patient's clinical features,

- to rotigotine (other extended release oral dopamine agonists remain relatively untested for developing significant augmentation with the expected continued long term use, but they can be considered).

For switching to an α2δ ligand, tapering off the dopaminergic agent is recommended with a brief period where the patient is taken off all medications. Alternatively, the non-dopaminergic agent can be added prior to or during the dopaminergic taper.

As augmentation or withdrawal may take days to weeks to resolve, evaluation of the efficacy of the new non-dopamine drug must wait until after this withdrawal period.

If this strategy fails then the patient is considered to have severe augmentation and should be treated accordingly.

b) Severe augmentation

Severe augmentation is augmentation that either does not fulfill the criteria for mild augmentation, (e.g., the total agonist dose exceeds recommended levels or the symptoms cause more than mild distress), or does not respond to treatment of mild augmentation as outlined above.

Initially, one of the following two approaches should be selected: **Substitution or cross titration**

The patient can be switched either to an α2δ calcium-channel ligand or to rotigotine, in very severe cases a high-potency opioid may be considered, bypassing α2δ ligands and rotigotine (see below). If the patient is switched to rotigotine then the shorter acting dopamine agonist can be discontinued and the rotigotine dose adjusted within approved dosage ranges. If the α2δ ligand is started it should be titrated to an effective dose (so the patient is temporarily on two RLS/WED medications). At that point, the dopamine agonist dose should be gradually reduced, warning the patient that a withdrawal is expected with temporary worsening of symptoms.

It must be considered that the ultimate objective is to ideally eliminate dopaminergic treatment, or at the very least ensure that it is at the lowest possible dose so as to minimize the risk of further augmentation. If the attempt to eliminate all dopaminergic treatment fails, combination therapy with a low-dose dopamine agonist and an α2δ ligand can be maintained.

10-day washout

The patient is gradually weaned off the dopamine drug, followed by a washout period of approximately 10 days without any drugs. At the end of the washout period, a new drug may be introduced. The advantages of the 10-day washout are that it enables the physician

to evaluate both the degree of RLS/WED symptoms on no medication and the benefits of any new drug treatment. Rarely will no drug treatment be needed. This option, however, can in some patients lead to transitory extremely severe RLS/WED symptoms and profound insomnia during the washout period. Education and counseling support is essential to help the patient with this process.

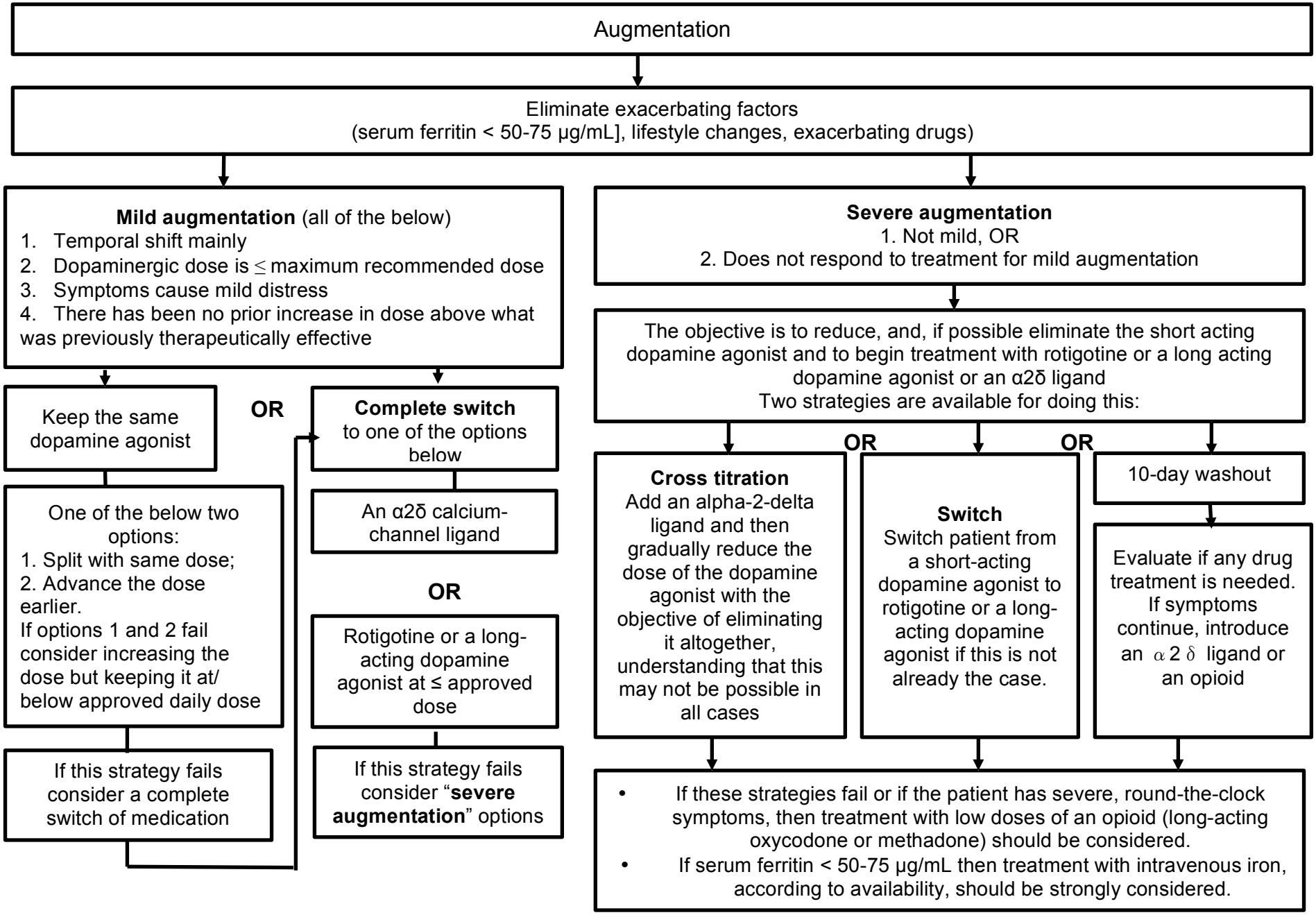
Consider an opioid

In patients with very severe symptoms, that is, symptoms with almost 24-hour duration, a low dose of an opioid (prolonged-release oxycodone[17] or methadone[13]) can be considered instead of an α2δ ligand. These drugs should also be considered if the above approaches fail. There are, however, special considerations regarding opioids and the physician should assess risk of addiction (family or personal history of alcohol or drug abuse, psychiatric comorbidities), non-medical diversion or comorbid medical issues (e.g., pre-existing severe constipation, prolonged QT_C). When patients are chosen appropriately, low dose opioid therapy is typically very effective and safe even when used for long-term therapy (based on considerable clinical experience). Educating the patient about the demonstrated efficacy and safety of these medications at the doses used in RLS/WED is essential. If the physician is uncomfortable prescribing opioids then they should refer the patient to a physician experienced in managing RLS/WED.

Iron therapy

If serum ferritin levels are < 50-75 µg/mL or transferrin saturation is less than 20%, then treatment with oral or intravenous iron, depending on the clinical situation, should be strongly considered. This can be undertaken in combination with any of the other options.

Figure 1: Augmentation treatment algorithm



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