



ChESA 8th
Chemical Engineering on Science and Applications

THE 5th ANNUAL INTERNATIONAL CONFERENCE SYIAH KUALA UNIVERSITY
(AIC - UNSYIAH)
IN CONJUNCTION WITH
THE 8th CHEMICAL ENGINEERING ON SCIENCE AND APPLICATION
(ChESA)

LIFE SCIENCES CHAPTER



AAC Dayan Dawood, Darussalam - Banda Aceh, Indonesia
September 9 - 11 , 2015



**Proceeding of the 5th Annual International Conference (AIC) Syiah
Kuala University 2015 in Conjunction with the 8th Chemical
Engineering Science & Applications (ChESA)
9-11 September 2015, Banda Aceh – Indonesia**

Editor in Chief : Dr. drh. Ummu Balqis, M.Si.
(Syiah Kuala University, Indonesia)

Editors : **Prof. Dr. drh. Darmawi, M.Si.**
(Syiah Kuala University, Indonesia)
Prof. Dr. Ir. Samadi, M.Sc.
(Syiah Kuala University, Indonesia)
Prof. Roselyn M. Butalid
(Mindanao State University, Philippines)
Associate Prof. Dr. Ororat Mongkolporn, Ph.D
(Kasetsart University, Thailand)
Prof. Dr. Dr. h.c. Evamarie Hey-Hawkins
(Universität Leipzig, Germany)
Prof. Dr. med. vet. Jean-Michel Hatt, MSc, Dipl ACZM, ECZM (Avian)
(University of Zurich, Switzerland)
Dr. Kazuaki Syutsubo
(National Institute for Environmental Studies, Japan)
Prof. Dr. Ir. H. Hasanuddin, M.S.
(Syiah Kuala University, Indonesia)
drh. Al Azhar, M. Kes.
(Syiah Kuala University, Indonesia)

ISSN: 2089-208X
Copyright © 2015
Printed September 2015

Message from the Rector



Assalamu'alaikum Wr. Wb.

Ladies and gentlemen, it is an honor indeed to open this conference, the 5th Annual International Conference (the 5th AIC) in conjunction with the 8th Chemical Engineering on Science and Application (the 8th ChESA) conference. On behalf of Syiah Kuala University or Unsyiah, I would like to extend a warm welcome to all participants and our speakers who are with us to make this a notable and exciting event.

This year, Unsyiah commemorates its 53rd anniversary. As part of the celebration, the university has held a number of events, including this interdisciplinary conference from September 9-11, 2015. At Unsyiah, we emphasize the excellence in education and research, and are also committed to innovation and technology. Today, we are facing more challenges in these spheres, therefore, as members of the academic community; we have a duty to find innovative research solutions for them. Hence, this conference is an excellent forum for experts, professionals, researchers, and students, to present, share, and discuss their knowledge and experiences with all of us. As a result, it is a privilege to host you, not just this year, but for years to come, to give and provide opportunities to contribute lasting and practical solutions to the challenges that confront us from time to time.

This conference includes keynote speeches, oral and poster parallel sessions on topics in the field of sciences, life sciences, engineering, social sciences, and ChESA. We thank our keynote and invited speakers for their contribution, time and support for this conference. Heartfelt appreciation goes to all the authors of the selected papers for their effort and hard work. I also thank the organizing committee of the conference for their exertion in making this event successful. I wish to encourage them to continue more events and other initiatives as well. To support and sustain important research linkage for dialogue and facilitate ideas exchange such as this will certainly generate many new discoveries in years to come.

Finally, I wish you a wonderful stay in Banda Aceh. Please enjoy our university's pleasant learning environment and our city's appealing offer in food and tourism. I am sure the committee of this conference extends their warm hospitality to make your brief stay positively memorable.

Thank you.

Prof. Dr. Ir. Samsul Rizal, M.Eng.

Message from the Chairman



Assalamu'alaikum Wr. Wb.

I take this occasion to cordially welcome all participants of the 5th Annual International Conference (or AIC) in conjunction with the 8th Chemical Engineering on Science and Application (or ChESA) conference. This conference is held in the heart of our campus, Syiah Kuala University or Unsyiah, Banda Aceh, from September 9 to September 11, 2015. Unsyiah, the home of 12 notable faculties and one school of postgraduate studies, is one of the major state universities in Indonesia. Its pleasant surroundings in a city with remarkable history are a spotlight for this congregation. We are assured that the 200 scientific participants contribute to productive discussions and exchanges that impact the success of this conference. Participants from 10 countries; Indonesia, Malaysia, Thailand, South Africa, Japan, Singapore, Taiwan, Germany, England, Australia countries have marked the conference to be in an international scope.

I would like to express my gratitude to the Research Institute of Syiah Kuala University or *Lembaga Penelitian (Lemlit)* and the committee members for helping us with full force in organizing the conference. The conference and proceedings are a credit to a large group of people and everyone should be proud of the outcome. There are four plenary speakers covering the different areas of the conference. From science and engineering, there is Prof. Dr. Evamarie Hey-Hawkins from University Leipzig, Germany. From ChESA, there is Dr. Kazuaki Syutsubo from the National Institute for Environmental Studies (NIES), Japan. From life sciences, there is Associate Professor Dr. Ororat Mongkolporn from Kasetsart University, Thailand. And finally from social sciences, there is Professor Dr. Patrick Daly from National University of Singapore. Their talks cover the full range of the conference topics.

We are delighted with the vast responses of 166 submissions from researchers and practitioners. The knowledge bases that we are aiming to generate on the conferences topics are overwhelming due to the involvement of these experts from various fields of studies. Their papers are published in the proceedings to provide permanent records of what has been presented. The proceedings are divided into Life Sciences, Engineering, Social Sciences, and ChESA sections, and the 158 papers published here exhibit the current state of development in all aspects of important topics that are instrumental to all researchers in the field. They have succeeded in bringing together various aspects of developments and innovations in knowledge and technology that will benefit not only the academic community, but society itself.

It is hoped that this conference does not only provide a member meet, but also offer a common platform for academia and practitioners to discuss issues related to their field of studies. We also wish everyone a pleasant stay in Banda Aceh and have a taste of our best traditional culinary.

Thank you,
Prof. Dr. drh. Darmawi, M.Si

CONTENT

EDITORIAL BOARD		Pages
MESSAGE FROM THE RECTOR		
MESSAGE FROM THE CHAIRMAN		
No	Scientific Paper	
	Keynote and Invited Speaker	1
1	SNP Mapping to Locate Anthracnose Resistance in <i>Capsicum</i> spp. <i>Orarat Mongkolporn (Thailand)</i>	2-5
2	Development of simple and cost-effective treatment system for municipal wastewater <i>Takashi Onodera, Kazuaki Syutsubo (Japan)</i>	6
3	The Importance of Chemistry for Nanotechnology <i>Evamarie Hey-Hawkins (Germany)</i>	7
4	Hybrid Catalytic-Plasma Reactor for Energy and Chemical Conversions <i>I. Istadi (Indonesia)</i>	8
5	Photocatalytic oxidation in phenol removal using Ru/TiO ₂ and Ru/Al ₂ O ₃ catalysts <i>Syaifulah Muhammad (Indonesia)</i>	9
	Agriculture	10
1	Microstructure and Optimization of Sweet Potato-Rice Simulated Chips <i>Adil Basuki Ahza (Indonesia), M. Arief Munandar (Indonesia), and Subarna Suryatman (Indonesia)</i>	11-15
2	Some Rice Varieties Tolerant to Nitrogen Deprivation <i>Muhammad Hatta (Indonesia), Rosmayati (Indonesia), Chairani Hanum (Indonesia), and Hamidah Hanum (Indonesia)</i>	16-19
3	Effect of Leaf Extract Sirih (<i>Piper betle</i> L.) and on Future Soaking Time Freshness of Flowers Rose (<i>Rosa sinensis</i> L.) <i>Devi Wahyuni (Indonesia), Rita Hayati (Indonesia), and Nurhayati (Indonesia)</i>	20-24
4	How to restore the Tropical Peat Swamp Forest in Aceh Province, Indonesia <i>Hairul Basri (Indonesia), Sufardi (Indonesia), Sugianto (Indonesia), Syamaun A Ali (Indonesia), Khairullah (Indonesia), and Ahmad Reza Kasuri (Indonesia)</i>	25-28
5	Effect of Corn Extract and Solution of PEG to Increase Viability and Vigour of Sweet Corn Seed Deterioration at Different Incubation Periods <i>Herma Julendri (Indonesia), Halimursyadah (Indonesia), and Hasanuddin (Indonesia)</i>	29-32
6	Fig Pollinating Wasp Transfers Nematodes into Figs of <i>Ficus racemosa</i> in Sumatra, Indonesia <i>Jauharlina (Indonesia), Rina Sriwati (Indonesia), Yusmaini (Indonesia), Natsumi Kanzaki (Japan), Stephen Compton (South Africa)</i>	33-37
7	Physiological Seed Performance of Local Aceh and National Release Variety of Rice (<i>Oryza sativa</i> L.) to Water Stress <i>Cut Nur Ichsan (Indonesia), Bakhtiar (Indonesia), Efendi (Indonesia), and Sabarudin (Indonesia)</i>	38-42
8	Application of Soil Conservation in Oil Palm Plantation <i>Halus Satriawan (Indonesia), Zahrul Fuady (Indonesia), and Zara Yunizar (Indonesia)</i>	43-46
9	Genetic Characterization and Estimation Variety Eight of Papaya Genotype <i>Siti Hafisah (Indonesia), Yusnizar (Indonesia), and Firdaus (Indonesia)</i>	47-49
10	Adaptation of Some Clones of Sweet Potato (<i>Ipomoea batatas</i> L.) in the Lowlands and the Use of Manure <i>Mardhiah Hayati (Indonesia), Sabaruddin (Indonesia), Efendi (Indonesia), Ashabul Anhar (Indonesia), Elly Kesumawati (Indonesia), and NurKamalia (Indonesia)</i>	50-54
11	Investigation of the Effect of Heat Moisture Treatment on Local Sweet Potato Starch Characteristics <i>Zaidiyah (Indonesia), and Lukmanul Hakim (Indonesia)</i>	55-57
12	Rejuvenation and Characterization of Local Rice Germplasm (<i>Oryza sativa</i> L.) Under Organic Cultivation System <i>Efendi (Indonesia), Bakhtiar (Indonesia), Sabaruddin Zakaria (Indonesia), and Syafruddin (Indonesia)</i>	58-62
13	Roots Bioassay of Upland Rice Varieties on Several Soil Moisture Gradients <i>Syarifa Mayly (Indonesia), A. Rauf (Indonesia), Chairani Hanum (Indonesia), and Hamidah Hanum (Indonesia)</i>	63-66
14	Compost Oil Palm and Indigenous Endophytic Fungi Effect on Basal Stem Rot in Oil Palm Seedling <i>Lisnawita (Indonesia), Hamidah Hanum (Indonesia), and Ahmad Rafiqi Tantawi (Indonesia)</i>	67-70
15	Colonization Ability of Biological Control Agent <i>Tricoderma</i> spp on Cocoa Pod and Seedling <i>Rina Sriwati (Indonesia), Tjut Khamzurni (Indonesia), Elvira Iskandar (Indonesia), and</i>	71-75

	<i>Mitra Tri Annisa Lestari (Indonesia)</i>	
16	Production and Physiological Characters of Soybean Varieties Under Drought Stress with Application of Nitrogen Sources <i>Yaya Hasanah (Indonesia), Tengku Chairun Nisa (Indonesia), Hapsoh (Indonesia), Hamidah Hanum (Indonesia)</i>	76-82
17	Exploration of Pulp and Husk of Gayo Arabica Coffee as Raw Material of Pectin – SWOT, Risk and Chemical Component Analysis <i>Ismail Sulaiman (Indonesia), MurnaMuzaifa (Indonesia), Dian Hasni (Indonesia), and Julius Munandar (Indonesia)</i>	83-87
18	Enhance the Growth and Flowering of Roses (<i>Rosa galica</i> L.) Due to Composted Waste Coffee Powder and Gibberellins Concentration <i>Elly Kesumawati (Indonesia), Feri Affriadi (Indonesia), and Mardhiah Hayati (Indonesia)</i>	88-91
19	The Effect of Biological Liquid Fertilizer Application on the Growth and Yield of Two Varieties Maize (<i>Zea Mays</i> L.) <i>Zikril Maulana (Indonesia), Zaitun (Indonesia), and Jumini (Indonesia)</i>	92-95
20	Radiosensitivity and the Influence of Gamma Rays Irradiation on Local Samosir Shallots <i>Mariati Sinuraya (Indonesia), Rosmayati (Indonesia), Hasanuddin (Indonesia), and Diana Sofia Hanafiah (Indonesia)</i>	96-99
21	The Increasing of N, P, and K Nutrient in Palm Oil Under Prenursery Seedling By Application of Palm Oil Waste Compost and Endofitic Microbes <i>Hamidah Hanum (Indonesia), Lisnawita (Indonesia), and Ahmad Rafiqi Tantawi (Indonesia)</i>	100-104
22	Effect of Organic Matters And Water Stress On Performance of Rice in Vegetative Phase Cut Nur Ichsan (Indonesia), Erida Nurahmi (Indonesia), Oktrya Rochmad (Indonesia), Bakhtiar (Indonesia), Efendi (Indonesia), and Sabarudin (Indonesia)	105-109
	Veterinary and Science	110
23	Pharmacokinetics Interaction of Corticosteroid with ^{99m} Tc-MDP Radiopharmaceuticals for Bone Imaging Agents and its Biodistribution Pattern <i>Isti Daruwati (Indonesia), Natalia Purwanti (Indonesia), and Aang Hanafiah Ws (Indonesia)</i>	111-115
24	The Analysis of Constraints and Opportunities Development of Livestock in Aceh Besar <i>Ikramuddin (Indonesia), Ghazali Syamni (Indonesia), Bambang Ali Nugroho (Indonesia), and Nuhfil Hanani (Indonesia)</i>	116-119
25	Biocompatibility of Chitosan/Collagen/PVA Nanocomposite Containing Calcium Apatite <i>Basuki Wirjosentono (Indonesia), M. Dimas Ekananda Dawandono (Indonesia), and Tamrin (Indonesia)</i>	120-124
26	Histamine Levels in Repeated Thawing Beef <i>Nurliana (Indonesia), Borgo Mauliy Nasution (Indonesia), Darmawi (Indonesia), and Sugito (Indonesia)</i>	125-128
27	Mucosal Mast Cells in Intestine of Chicken (<i>Gallus domesticus</i>) Infected Naturally by <i>Ascaridiagalli</i> Adult Worm <i>Ummu Balqis (Indonesia), Masda Admi (Indonesia), Darmawi (Indonesia), and Muhammad Hambal (Indonesia)</i>	129-131
28	Inhibition of <i>Salmonella</i> sp. Growth in Comparison with Antibiotics and Pineapple (<i>Ananas comosus</i>) Squeeze <i>Masda Admi (Indonesia), Erina (Indonesia), Azhari (Indonesia), Ummu Balqis (Indonesia), Muhammad Hambal (Indonesia), and Darmawi (Indonesia)</i>	132-135
29	Morphology and Parasitaemia Development of <i>Plasmodium berghei</i> in Balb/c Mice (<i>Musmusculus</i>) <i>Rosnizar (Indonesia), and Kartini Eriani (Indonesia)</i>	136-138
30	Toll-Like Receptor 3-4 Expression Decrease in BALB/c Diabetic Mouse Models <i>Muhaimin Rifa'i (Indonesia), Aris Soewondo (Indonesia), and M. Sasmito Djati (Indonesia)</i>	139-141
	Fisheries and Aquaculture	142
31	Comparison of Bacteriocins Produced by Probiotic Bacteria from Giant Tiger Prawn (<i>Panaeus monodon</i>) and Giant Freshwater Prawn (<i>Macrobrachium rosenbergii</i>) <i>Feliatra (Indonesia), Widya Rahmy Utamy (Indonesia), and Hilwan Yuda Teruna (Indonesia)</i>	143-147
32	Vegetation Structure and Potential Gross Primary Productivity of Mangrove Forest in Kuala Indragiri Coastal <i>Mariana (Indonesia), Feliatra Felix (Indonesia), Sukendi (Indonesia), and Syafruddin Nasution (Indonesia)</i>	148-151
33	Quercetin and Allicinas Prophylactic Herbs for Brackishwater Tilapia in Periphyton Nursery System <i>Ibnu Sahidhir (Indonesia), Abdul Razaq (Indonesia), M. Yasir (Indonesia), and Abidin Nur (Indonesia)</i>	152-156
34	The Growth of Wild and Hatchery Juvenile Tiger Grouper (<i>Epinephelus fuscoguttatus</i>) Based on Different Feeds <i>Muhammadar A. Abbas (Indonesia), Firdus Basyah (Indonesia), and Asmawati M.</i>	157-161

	<i>Sail(Indonesia)</i>	
35	The Potential of Giving Leaf Extract <i>Menthapiperitaas</i> Bioformalinin the Preservation of Fresh Fish Depik (<i>Rasboratawarensis</i>) <i>Safrida (Indonesia), M. Ali S. (Indonesia), Yunura Anggarawati (Indonesia)</i>	162-165
36	Belacan Depik (<i>Rasboratawarensis</i>): A Fermented Fresh Water Fish of Gayonese <i>Murna Muzaifa (Indonesia)</i>	166-168
	Medicine and Health	169
37	Postpartum Coccydynia: an Anatomy Overview <i>Reza Maulana (Indonesia), Nur Wahyuniati (Indonesia), and Imai Indra (Indonesia)</i>	170-172
38	Survey of the cardiovascular drug interactions on geriatrics at internal medicine ward of RSUDZA Banda Aceh <i>Hijra Novia Suardi (Indonesia), and Suryawati (Indonesia)</i>	173-176
39	Pharmacologic Aspect of Neuropathic Pain <i>Endang Mutiawati (Indonesia), Imai Indra (Indonesia), Syahrul (Indonesia), and Mulyadi (Indonesia)</i>	177-182
40	The Influence of MMP-3 towards MMP-9 among Emphysematous Patients from Gingival Crevicular Fluid and Sputum <i>Mulkan Azhary (Indonesia), Muhammad Amin (Indonesia), Soetjipto (Indonesia), Mulyadi (Indonesia), and Sunnati (Indonesia)</i>	183-186
41	Screening of Degenerative Diseases and Quality of Life among Elderly People in Posyandu Lansia Medan Amplas Sub-Districts, Medan <i>Juliandi Harahap (Indonesia), and Lita Sri Andayani (Indonesia)</i>	187-191
42	Inflammation and the Migration of Mesenchymal Stem Cell <i>Reza Maulana (Indonesia), Nur Wahyuniati (Indonesia), and Imai Indra (Indonesia)</i>	192-195
43	Healthy House as Indicator to Realize Healthy City and its Relationship with the Role of Community in Medan City <i>Lita Sri Andayani (Indonesia), and Juliandi Harahap (Indonesia)</i>	196-200
44	The Use of Herbal Medicine in Children <i>Suryawati and Hijra Novia Suardi (Indonesia)</i>	201-204
45	The Correlation Between the Level of Diabetic Patients' Knowledge and Quality of Life in Patients with Type 2 Diabetes Mellitus at Haji Adam Malik Hospital Medan <i>Rina Amelia (Indonesia)</i>	205-210
46	Analysis of Factors Affecting The Quality of Life in Vitiligo Patients at Dermato-Venereology Polyclinic dr. Zainoel Abidin General Hospital, Banda Aceh <i>Fitria (Indonesia), Vera D. Mulia (Indonesia), and Hafni A. (Indonesia)</i>	211-214
47	Correlation Between Management of Balanced Menu and Weight Gain on Pregnant Women Trimester III in Rural Hospital Montasik 2015 <i>Halimatussakdiah (Indonesia)</i>	215-221
48	Barrier for Psychologist's Provision of Service <i>Lely Safrina (Indonesia)</i>	222-224
49	Characteristic of Single Epitope on GP350/220 Protein that Promising for Nasopharyngeal Cancer Vaccine Seed Production in <i>Escherichia Coli</i> <i>Widodo (Indonesia)</i>	225-227
50	Cost Effectiveness Analysis of Antibiotic Therapy in Appendectomy Prophylactic at dr. Zainoel Abidin Hospital Banda Aceh <i>Suci M. Rahmah (Indonesia), AzizahVonna (Indonesia), Khairan (Indonesia), and Rinaldi Idroes (Indonesia)</i>	228-230
51	Profile of Thalassaemia Patient in Zainoel Abidin Hospital at Aceh <i>Salwani D. (Indonesia), and Riswan M. (Indonesia)</i>	231-234
52	Antibacterial Activities of <i>n</i> -hexane Extract <i>Casiaalata</i> Leaves <i>Murniana (Indonesia), Mustanir (Indonesia), Binawati Ginting (Indonesia), Ega Rizki (Indonesia), and Kartini Hasballah (Indonesia)</i>	235-237
53	Antimicrobial Peptides: Their Role in Innate Immune System and Usage in Future Drug Development <i>Tristia Rinanda(Indonesia)</i>	238-243

Keynote and Invited Speakers:

Associate Prof. Dr. Ororat Mongkolporn, Ph.D
(Kasetsart University, Thailand)

Prof. Dr. Dr. h.c. Evamarie Hey-Hawkins
(Universität Leipzig, Germany)

Dr. Kazuaki Syutsubo
(National Institute for Environmental Studies, Japan)

Pharmacologic Aspect of Neuropathic Pain

¹Endang Mutiawati, ²Imai Indra, ³Syahrul, ⁴*Mulyadi

¹Department of Neurology, Faculty of Medicine, Syiah Kuala University, Darussalam, Banda Aceh 23111, Indonesia;

²Department of anesthesiology, Medical Faculty, Syiah Kuala University, Banda Aceh 23111, Indonesia;

³Faculty of Medicine, Syiah Kuala University, Darussalam, Banda Aceh 23111, Indonesia;

⁴Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Syiah Kuala University, Darussalam, Banda Aceh 23111, Indonesia;

Corresponding author : mul.0862@gmail.com

Abstract

Neuropathic pain is pain arising from nerve damage to the conductive pathways of pain (ranging from nociceptors to post central gyrus). Neuropathic pain can be caused by 1) Carcinomas, 2) Trauma/compressive, 3) Congenital, 4) Immunomediated, 5) Infection, 6) Metabolic disorders, 7) nutritional deficiency, 8) Toxin, 9) Lesion, 10) Vasculitis, 11) Connective tissue disorders. To date, the pathophysiology of neuropathic pain can not be explained thoroughly, this problem leads to the treatment which has not given satisfactory results as expected. There are many types of drugs has been used for the treatment of neuropathic pain, and they are generally aimed to stop the flow of impulses in the nervous system which was activated as a result of ectopic generators in areas experiencing nerve injury. These drugs work in several locations such as: drugs that works on 'sodium channel voltage gate' (i.e Carbamazepine group), drugs that works on 'calcium channel' (i.e Gabapentin and Pregabalin), and also drugs that works on 'the synapses gap' (i.e Tricyclic class). Besides drugs that inhibit pain impulses propagation, the treatment of neuropathic pain also include drugs that have the ability of nervous system regeneration such as methylcobalamin group. The rationale of the use of this kind of drugs is that this drug expected to regenerate the damage of the nervous system damage which is lead to decrease the ectopic generator activity, the end result is the reduction of neuropathic pain experienced by patients.

Key words: neuropathic pain, pharmacologic, regeneratif

Introduction

Neuropathic pain is common, greatly impairs quality of life and has a high economic impact on society: the Institute of Medicine reports that at least 116 million American adults suffer from chronic pain, and estimates for people suffering from neuropathic pain are as high as 17.9%. Co-morbidities such as poor sleep, depression and anxiety are common in neuropathic pain patients, leading to unresolved arguments about whether pain causes mood and sleep changes or whether individuals with mood and sleep disorders are at a higher risk of developing pain (Hehn *et al.*, 2012). Neuropathic pain (NP) is estimated to afflict as high as 7–8% of the general population in Europe (Attal *et al.*, 2010), an estimated prevalence of 5% to 7% in France, compared with 20% to 31% for chronic pain (Delorme *et al.*, 2011) and It is a common condition with an overall prevalence between 0.9 and 8.0% (Athanasakis *et al.*, 2013).

The International Association for the Study of Pain (IASP) defines neuropathic pain (NP) as pain "initiated or caused by a primary lesion or dysfunction in the nervous system". It is estimated to afflict millions of people worldwide, although precise figures are not available. Neuropathic pain can be caused by a number of different diseases (e.g., diabetes mellitus, herpes zoster, human immunodeficiency virus [HIV] infection), medical interventions (e.g., chemotherapy, surgery), and injuries (e.g., brachial plexus avulsion) cause NP by producing lesions in somatosensory pathways in the peripheral or central nervous system (Dworkin *et al.*, 2007; O'Connor & Dworkin, 2009). The management of patients with NP is complex and response to existing treatments is often inadequate. Even with well-established NP medications, effectiveness is unpredictable, dosing can be complicated, analgesic onset is delayed, and side effects are Common (Dworkin *et al.*, 2007; Attal *et al.*, 2010).

Materials and Methods

This article review form articles related with the pharmacologic aspect of neuropathic pain. All data contained in this article is the result of a number of articles search.

Results and Discussion

In 2006, the European Federation of Neurological Societies (EFNS) produced the first guidelines on pharmacological treatment of NP. Since 2006, new randomized controlled trials (RCTs) have appeared in various NP conditions, justifying an update (Dworkin *et al.*, 2007; Attal *et al.*, 2010).

Pharmacological treatment is the mainstream in post-herpetic neuralgia (PHN), diabetic peripheral neuropathic pain (DPNP), central post-stroke pain (CPSP), trigeminal neuralgia (TN), complex regional pain syndrome (CRPS), cancer pain, failed back syndrome etc, while polypharmacy is still the major prescriptions facing such kind of miserable patients. The tricyclic antidepressants (TCA), gamma-aminobutyric acid (GABA), voltage-dependent calcium channel blockers, selective non-epinephrine reuptake inhibitor (SNRI), opioid or morphine etc, are still evidence-based medicines (EBM) but with different outcome for individuals (Yang *et al.*, 2012). Use of antiepileptics with demonstrated efficacy as first-line therapy has increased in neuropathic pain (Hall *et al.*, 2013).

Table 1. Stepwise Pharmacologic Management of Neuropathic Pain (O'Connor & Dworkin, 2009)

Step 1

- Assess pain and establish the diagnosis of NP, if uncertain about the diagnosis, refer to a pain specialist or neurologist
- Establish and treat the cause of NP; if uncertain about availability of treatment addressing NP etiology, refer to appropriate specialist
- Identify relevant comorbidities (e.g., cardiac, renal, or hepatic disease, depression, gait instability) that might be relieved or exacerbated by NP treatment, or that might require dosage adjustment or additional monitoring of therapy
- Explain the diagnosis and treatment plan to the patient, and establish realistic expectations

Step 2

- Initiate therapy of the disease causing NP, if applicable
- Initiate symptom treatment with one or more of the following:
 - ✓ Antidepressant medication: either secondary amine TCA (nortriptyline, desipramin) or SSNRI (duloxetine, venlafaxine)
 - ✓ Calcium channel $\alpha_2\text{-}\delta$ ligand: either gabapentin or pregabalin
 - ✓ For patients with localized peripheral NP: topical lidocaine used alone or in combination with 1 of the other first-line therapies
 - ✓ For patients with acute NP, neuropathic cancer pain, or episodic exacerbations of severe pain, and when prompt pain relief during titration of a first-line medication to an efficacious dosage is required, opioid analgesics or tramadol may be used alone or in combination with 1 of the first-line therapies.
- Evaluate patient for nonpharmacologic treatments, and initiate if appropriate

Step 3

- Reassess pain and health-related quality of life frequently
- If substantial pain relief (e.g., average pain reduced to NRS $\leq 3/10$) and tolerable side effects, continue treatment.
- If partial pain relief (e.g., average pain remains $\geq 4/10$) after an adequate trial, add 1 of the other first-line medications
- If no or inadequate pain relief (e.g., $<30\%$ reduction) at target dosage after an adequate trial, switch to an alternative first-line medication

Step 4

- If trials of first-line medications alone and in combination fail, consider second-line medications or referral to a pain specialist or multidisciplinary pain Center

NP-neuropathic pain; NRS-numeric rating scale; SSNRI-selective serotonin and norepinephrine reuptake inhibitor; TCA-tricyclic antidepressant. Reprinted with permission from Pain.

Three classes of medications were recommended as firstline treatments: antidepressants with both norepinephrine and serotonin reuptake inhibition (TCAs and selective serotonin and norepinephrine reuptake inhibitors [SSNRIs]), calcium channel 2- ligands (gabapentin and pregabalin), and topical lidocaine (lidocaine patch 5%). Opioids and tramadol were recommended as generally second-line treatments, except in certain specific clinical situations in which it was recommended that first-line use could be considered. A number of medications were considered third-line choices (O'Connor & Dworkin, 2009). Based on efficacy and safety, pregabalin is considered a first-line drug together with gabapentin in the treatment of central pain (Finnerup & Jensen, 2007).

The guidelines acknowledge that a combination of medications with efficacy for neuropathic pain may provide greater analgesia than use of individual medications as monotherapy, although such combination therapy will often be associated with increased side effects, inconvenience, risk of drug interactions, and cost. Nevertheless, because 50% of patients in Neuropathic Pain trials of efficacious medications typically achieve satisfactory pain relief, many patients in clinical practice will require treatment with a combination of medications. Such combination therapy was incorporated into a

stepwise management strategy for patients with partial responses to treatment with first-line medications (O'Connor & Dworkin, 2009).

Table 2. Summary of the results of Randomized Clinical Trials Involving First and Second-Line Medications for Patients With Neuropathic Pain (O'Connor & Dworkin, 2009)

	TCA	Duloxetine	Venlafaxine	Gabapentin	Pregabalin	Topical lidocaine 5% patch	Opioid analgesics	Tramadol
Peripheral NP								
- Painful DPN	(+)	(+)	(+)	Both	Both	-	(+)	(+)
- PHN	(+)	-	(-)	(+)	Both	(+)	(+)	(+)
- Painful polyneuropathy	(+)	-	(+)	(+)	-	(+)	(+)	(+)
- Phantom limb pain	(-)	-	-	Both	-	-	(+)	(+)
- Postmastectomy pain	(+)	-	(-)	-	-	-	-	-
- GBS	-	-	-	(+)	-	-	-	-
- Neuropathic cancer pain	(-)	-	-	(+)	-	-	-	-
- CPRS type I	-	-	-	(-)	-	-	-	-
- Chronic lumbal root pain	(-)	-	-	-	-	-	(-)	-
- Chemotherapy induced neuropathy	(-)	-	-	(-)	-	-	-	-
- HIV Neuropathy	(-)	-	-	(-)	-	-	-	-
Central NP								
- Central poststroke pain	(+)	-	-	-	(+)	-	-	-
- Spinal cord injury pain	(-)	-	(+)	(+)	-	-	-	-

The NeuPSIG guidelines note that few medications have been found to be efficacious in neuropathic pain originating from a lesion in the central nervous system. RCTs have demonstrated efficacy for TCAs in central poststroke pain, and for calcium channel α_2 - δ ligands in spinal cord injury and poststroke central neuropathic pain. The Canadian Pain Society created 4 levels of recommendation, with first- and second-line medications differentiated by "the quality of evidence and the evidence of efficacy" based on NNTs. Medications were classified as third-line treatments if they have good evidence of efficacy, but require specialized monitoring and follow-up not required of drugs at the other levels. Fourth-line medications were described as having "at least 1 positive RCT, but required further study" (O'Connor & Dworkin, 2009).

As with the NeuPSIG and Canadian Pain Society guidelines, the EFNS guidelines grade the level of evidence for different available treatments. However, unlike the other 2 sets of guidelines, separate recommendations were made for the treatment of patients with painful polyneuropathies (including painful diabetic peripheral neuropathy), postherpetic neuralgia, trigeminal neuralgia, and central neuropathic pain. Consistent with the NeuPSIG and Canadian Pain Society guidelines, the EFNS guidelines recommended gabapentin, pregabalin, and TCAs as first-line treatments for painful polyneuropathies, postherpetic neuralgia, and central neuropathic pain (Moulin *et al.*, 2007; O'Connor & Dworkin, 2009; Rhodes, 2011).

Table 3. Comparison of Neuropathic Pain Treatment Guidelines, Excluding Trigeminal Neuralgia (O'Connor & Dworkin, 2009).

Medication Class	NeuPSIG Guidelines	CPS Guidelines	EFNS Guidelines
Tricyclic antidepressants	First line	First line	First line for PPN, PHN, and CP
Calcium channel α_2 - δ ligands (gabapentin and pregabalin)	First line	First line	First line for PPN, PHN, and CP
SSNRIs (duloxetine and venlafaxine)	First line	Second line	Second line for PPN
Topical lidocaine	First line for localized peripheral NP	Second line for localized peripheral NP	First line for PHN if small area of pain/allodynia
Opioid analgesics	Second line except in selected circumstances [†]	Third line	Second-third-line for PPN, PHN, and CP
Tramadol	Second line except in selected circumstances [†]	Third line	Second-third-line for PPN and PHN

CP = central pain; CPS = Canadian Pain Society; EFNS = European Federation of Neurological Societies; NeuPSIG = Neuropathic Pain Special Interest Group; NP = neuropathic pain; PHN = postherpetic neuralgia; PPN = painful polyneuropathy; SSNRIs = selective serotonin and norepinephrine reuptake inhibitors.

*Only medications considered first or second-line in 1 of the guidelines are presented.

[†]Opioid analgesics and tramadol were considered first-line options in the following circumstances: for the treatment of acute NP, episodic exacerbations of severe NP, neuropathic cancer pain, and during titration of a first-line medication in patients with substantial pain.

Other EFNS recommendations for painful polyneuropathies were duloxetine and venlafaxine as second-line treatment ("because of moderate efficacy"), and opioids, tramadol, and lamotrigine as "second-/thirdline therapy." Additional recommendations for postherpetic neuralgia were topical lidocaine as a first-line treatment for patients with localized pain and allodynia, and opioids, tramadol, capsaicin, and valproic acid as second-line treatment options. "Second-/third-line" treatment options for patients with central neuropathic pain were lamotrigine, opioids, and cannabinoids (Moulin *et al.*, 2007; O'Connor & Dworkin, 2009; Rhodes, 2011).

Two drugs have been approved for neuropathic pain in the US – pregabalin and duloxetine – but neither of these afford complete relief, even when used in combination (Vinik & Cassellini, 2012). In addition, several novel drug treatments such as botulinum toxin, capsaicin patch and lacosamide have been also used for neuropathic pain therapy. Table 5 summarizes the major pharmacological treatments for neuropathic pain and their analgesia mechanisms (Xu *et al.*, 2012).

Table 4. Major pharmacological treatment for neuropathic pain and their basic mechanisms (Xu *et al.*, 2012)

Compound	Mode of action
Antidepressant	
- Nortriptyline	Inhibition of both serotonin and norepinephrine reuptake
- Desipramine	Inhibition of both serotonin and norepinephrine reuptake
- Duloxetine	Inhibition of both serotonin and norepinephrine reuptake
- Venlafaxine	Inhibition of both serotonin and norepinephrine reuptake
Anticonvulsants	
- Gabapentin	Decreases release of glutamate, norepinephrine and substance P, with ligands on $\alpha 2-\delta$ subunit of voltage
- Pregabalin	Decreases release of glutamate, norepinephrine and substance P, with ligands on $\alpha 2-\delta$ subunit of voltage
- Lacosamide	Decreases release of presynaptic transmitter inhibition of voltage-gated sodium channel
Opioid agonists	
- Morphine	μ -receptor agonism
- Oxycodone	μ -receptor agonism
- Methadone	μ -receptor agonism, κ -receptor antagonism
- Levorphanol	μ -receptor agonism
- Tramadol	μ -receptor agonism, inhibition of norepinephrine and serotonin reuptake
Topical therapy	
- 5% lidocaine patch	Block of sodium channel
- High dose capsaicin patch	Damage of nociceptive sensory axons, a highly selective activating ligand for TRPV1
- Botulinum toxin	Inhibition of both the exocytosis of acetylcholine and some other neurotransmitter

Pregabalin reduces the enhanced noxious stimulus-induced spinal release of glutamate seen in neuropathic rats (Kumar *et al.*, 2010). Intranasal or intrathecal pregabalin relieves neuropathic pain behaviours, perhaps due to pregabalin's effect upon anterograde CaV $\alpha 2\delta$ -1 protein trafficking from the DRG to the dorsal horn. Intranasal delivery of agents such as pregabalin may be an attractive alternative to systemic therapy for management of neuropathic pain states (Martinez *et al.*, 2012). The anti-allodynic effects of gabapentin may be caused by upregulation of IL-10 expression in the spinal cord, which leads to inhibition of the expression of pro-inflammatory cytokines in the spinal cords (Lee *et al.*, 2013).

Capsaicin is a transient receptor potential vanilloid-1 agonist, which increases the intracellular calcium ion concentration. This triggers calcium-dependent protease enzymes causing cytoskeletal breakdown and leads to the loss of cellular integrity and 'defunctionalization' of nociceptor fibres. Efficacy and therapeutic effect has been shown in several clinical studies of PHN and HIV-DSP. The high-concentration capsaicin patch and its practical application are different from low-concentration creams; one application can help for up to 3 months (Irving *et al.*, 2011; Webster *et al.*, 2012; Baranidharan *et al.*, 2013). A single 30-minute application of NGX-4010 (Capsaicin 8% patch) provides significant pain relief for at least 12 weeks in patients with HIV-DSP and is well tolerated (Simpson *et al.*, 2008; Brown *et al.*, 2013).

Activation of TRPV1 by capsaicin results in sensory neuronal depolarization, and can induce local sensitization to activation by heat, acidosis, and endogenous agonists. Topical exposure to capsaicin leads to the sensations of heat, burning, stinging, or itching. High concentrations of capsaicin or repeated applications can produce a persistent local effect on cutaneous nociceptors, which is best

described as defunctionalization and constituted by reduced spontaneous activity and a loss of responsiveness to a wide range of sensory stimuli (Anand & Bley, 2011; Bley, 2013).

Conclusions

All guidelines recommend TCAs, gabapentin, and pregabalin as first-line treatment options for patients with neuropathic pain (excluding trigeminal neuralgia). The NeuPSIG guidelines recommend duloxetine and venlafaxine as first-line treatment options, but the Canadian Pain Society and EFNS guidelines recommend these SSNRIs as second-line options for patients with painful polyneuropathies. Clinicians need to consider the advantage and disadvantage of these managements to avoid ineffective treatments, maximize curing proven beneficial in clinical trials, and minimize the side effect of therapies. To improve the current management of patients with neuropathic pain, evidence-based basic studies should be made for pharmacological approaches to guide the managements in the future.

References

- Anand, P. & Bley, K., 2011. Topical Capsaicin for pain management: therapeutic potential and mechanisms of action of the new high-concentration capsaicin 8% patch. *British Journal of Anaesthesia*, 107(4): 490-502.
- Athanasakis, K., Petrakis, L., Karampli, E., Vitsou, E., Lyras, L., Kyriopoulos, J., 2013. Pregabalin versus Gabapentin in the Management of Peripheral Neuropathic Pain Associated with Post-herpetic Neuralgia and diabetic neuropathy: a cost effectiveness analysis for the Greek Healthcare setting. *BMC Neurology*, 13:56.
- Attal, N., Cruccu, G., Baron, R., Haanpaa, M., Hansson, P., Jensen, T.S., Nurmikko, T., 2010. EFNS Guidelines on the pharmacological treatment of neuropathic pain: 2010 revision. *European Journal of Neurology*, 17: 1113-1123.
- Baranidharan, G., Das, S., Bhaskar, A., 2013. A review of the high-concentration capsaicin patch and experience in its use in the management of neuropathic pain. *Theurapeutic Advances in Neurological Disorders*, 6(5): 287-297.
- Bley, K., 2013. Effects of Topical Capsaicin on Cutaneous Innervation: Implications on Pain Management. *The Open Pain Journals*, 6: 81-94.
- Brown, S., Simpson, D.M., Moyle, G., Brew, B.J., Schifitto, G., Larbalestier, N., et al., 2013. NGX-4010, a Capsaicin 8% patch, for the treatment of the painful HIV-associated distal sensory polyneuropathy: integrated analysis of two phase III, randomised controlled trial. *AIDS Research and Therapy*, 10: 5.
- Delorme, C., Navez, M.L., Legout, V., Deleens, R., Moysse, D., 2011. Treatment of Neuropathic Pain with 5% lidocaine-medicated plaster: five years of clinical experience. *Pain Res Manage*, Vol 16, No 4.
- Dworkin, R.H., O'Connor, A.B., Backonja, M., Farrar, J.T., Finnerup, N.B., Jensen, T.S., et al., 2007. Pharmacologic Management of Neuropathic pain: Evidence-based Recommendations. *Pain*, 132: 237-251.
- Finnerup, N.B. & Jensen, T.S., 2007. Clinical use of pregabalin in the management of central neuropathic pain. *Neuropsychiatric Disease & Treatment*, 3(6): 885-891.
- Hall, G.C., Morant, S.V., Carroll, D., Gabriel, Z.L., McQuay, H.J., 2013. An Observational descriptive study of the epidemiology and treatment of neuropathic pain in a UK general population. *BMC Family Practice*, 14: 28.
- Hehn, C.A., Baron, R., Woolf, C.J., 2012. Deconstructing the Neuropathic pain Phenotype to Reveal Neural Mechanism. *Neuron*, 73(4): 638-652.
- Irving, G.A., Backonja, M., Rauck, R., Webster, L.R., Tobias, J.K., Vanhove, G.F., 2011. NGX-4010, a Capsaicin 8% dermal patch, administered alone or in combination with systemic neuropathic pain medications, reduces pain in patients with postherpetic neuralgia. *Clinical Journal Pain*.
- Kumar, N., Laferrriere, A., Yu, J.S.C., Leavit, A., Coderre, T.J., 2010. Evidence that pregabalin reduces neuropathic pain by inhibiting the spinal release of glutamate. *Journal of Neurochemistry*, 113: 552-561.
- Lee, B., Jun, I., Kim, S., Park, J.Y., 2013. Intrathecal Gabapentin increases Interleukin-10 Expression and Inhibits pro-inflammatory Cytokines in a rat model of neuropathic pain. *J Korean Med Sci*, 28: 308-314.
- Martinez, J.A., Kasamatsu, M., Rosalez-Hernandez, A., Hanson, L.R., Frey, W.H., Toth, C.C., 2012. Comparison of central versus peripheral delivery of the pregabalin in neuropathic pain states. *Molecular Pain*, 8: 3.
- Moulin, D.E., Clark, A.J., Gilron, I., Ware, M.A., Watson, C.P.N., Sessle, B.J., et al., 2007. Pharmacological Management of chronic Neuropathic Pain – Consensus Statement and guidelines from the Canadian Pain Society. *Pain Res Manage*, Vol 12: No 1.
- O'Connor, A.B. & Dworkin, R.H., 2009. Treatment of Neuropathic Pain: An Overview of recent Guidelines. *The American Journal of Medicine*, 122: S22-S32.
- Rhodes, C., 2011. Update on Therapies for Neuropathic Pain. *The Pain Practitioner*, Vol 21: No 3.
- Simpson, D.M., Brown, S., Tobias, J., 2008. Controlled trial of high-concentration capsaicin patch for the treatment of painful HIV neuropathy. *Neurology*, 70: 2305.
- Vinik, A.I. & Casellini, C.M., 2013. Guidelines in the management of diabetic nerve pain: clinical utility of pregabalin. *Diabetics, Metabolics syndrome and Obesity: Target and therapy*, 6: 57-78.
- Vranken, J.H., 2009. Mechanisms and Treatment of Neuropathic Pain. *Central Nervous System Agents in Medicinal Chemistry*, 9: 71-78.
- Webster, L.R., Peppin, J.F., Murphy, F.T., Tobias, J.K., Vanhove, G.F., 2012. Tolerability of NGX-4010, a capsaicin 8% patch, in conjunction with three topical anesthetic formulations for the treatment of neuropathic pain. *Journal of Pain Research*, 5: 7-13.
- Xu, B., Descalzi, G., Ye, H., Zhuo, M., Wang, Y., 2012. Translational investigation and treatment of neuropathic pain. *Molecular Pain*, 8: 15.
- Yang, C.M., Chen, N.C., Shen, H.C., Chou, C.H., Yeh, P.S., Lin, H.J., et al., 2012. Guideline of Neuropathic Pain Treatment and Dilemma from Neurological Point of View. *Acta Neurologica Taiwanica*, Vol 21: No 3.




The 5th Annual
INTERNATIONAL Conference (AIC 2015)
in conjunction with
The 8th Chemical Engineering on
Science and Application (ChESA 2015)

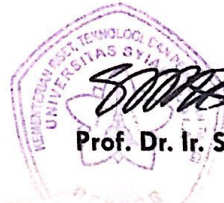

Hereby acknowledge the participation and contribution to :

Mulyadi
as
Presenter

in Banda Aceh - Indonesia, September 9 - 11, 2015



Prof. Dr. drh. Darmawi, M.Si
Chair Person



Prof. Dr. Ir. Samsul Rizal, M.Eng
Rector