

Original Article

Analysis on Composition Rules of Chinese Patent Drugs Treating Pain-Related Diseases Based on Data Mining Method*

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ABSTRACT **Objective:** To analyze the composition rules of oral prescriptions in the treatment of headache, stomachache and dysmenorrhea recorded in National Standard for Chinese Patent Drugs (NSCPD) enacted by Ministry of Public Health of China and then make comparison between them to better understand pain treatment in different regions of human body. **Methods:** Constructed NSCPD database had been constructed in 2014. Prescriptions treating the three pain-related diseases were searched and screened from the database. Then data mining method such as association rules analysis and complex system entropy method integrated in the data mining software Traditional Chinese Medicine Inheritance Support System (TCMISS) were applied to process the data. **Results:** Top 25 drugs with high frequency in the treatment of each disease were selected, and 51, 33 and 22 core combinations treating headache, stomachache and dysmenorrhea respectively were mined out as well. **Conclusions:** The composition rules of the oral prescriptions for treating headache, stomachache and dysmenorrhea recorded in NSCPD has been summarized. Although there were similarities between them, formula varied according to different locations of pain. It can serve as an evidence and reference for clinical treatment and new drug development.

KEYWORDS Chinese patent drug, headache, stomachache, dysmenorrhea, pain, Traditional Chinese Medicine Inheritance Support System, formulating principle

Pain, one of the most common clinical symptoms, is a complex physiological and mental activity. Pain syndrome is the earliest human feelings and understanding of disease. CM regards removing obstructions and nourishing body as the main treatment principle for pain syndrome based on the theory of "obstruction and malnutrition leading to pain". Although removing obstructions and nourishing body is the general principle of treatment, the specific medication is not the same because of the pain may lie on different sites.⁽¹⁾ National Standard for Chinese Patent Drugs (NSCPD) enacted by Ministry of Public Health of China is the national standard of Chinese patent drugs, which includes 4,052 kinds of Chinese patent medicines (CPMs). This standard not only regulates the quality standard of CPM, but also represents main trend of clinical application. Analysis on the standard could provide abundant reference material for clinical medication and effective carrier for summing up the law of disease prevention.⁽²⁾

Data mining technology has been widely used in the field of CM, and data mining analysis of prescription is one of the important areas.⁽³⁻⁷⁾ Excavation study on

abundant CM prescription data using data mining techniques could fully resolve component law of disease prevention, and provide important reference for prescription drug screening studies on new drug in CM.

Our group had built a structured database for CPMs,⁽⁸⁾ and developed a data mining software for composition rule exploration of CM. This software integrates the mining methods including general statistical method, text mining, association rules analysis, complex system entropy method, etc. It has been widely used in the aspects such as data mining of famous doctors' case, analysis of component law,

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*Supported by the National Nature Science Foundation of China (Nos. 81330086, 81203005), and the Fundamental Research Funds for the Central Public Welfare Research Institutes (No. ZZ070830)

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DOI: <https://doi.org/10.1007/s11655-017-2957-z>

and is a powerful tool for the mining and analysis of component law of prescription.⁽⁹⁻¹³⁾ Analysis on the existing CPMs using this software could clarify and summarize the current composition rule of the general rules of proprietary CM, and guide the clinical practice and drug development. In this paper, in order to further study on the composition law of CPMs treating pain, oral medicine prescription preparations with pain therapeutic effect recorded in structured databases for CPMs were analyzed based on auxiliary platform for CM. Depending on the site of pain, prescriptions treating headache, stomachache, dysmenorrhea, corresponding higher, middle and lower on the body, were selected as the research object, and the component law was summarized and analyzed by data mining method. Finally, the different principles and methods for pain management were clarified.

METHOD

Source of Recipes

NSCPD database containing 4,052 Chinese patent drugs had been built previously,⁽⁶⁾ data in which had been cleansed to guarantee its quality. Therefore, to get the oral medicine prescription preparations treating headache, stomachache and dysmenorrhea, the NSCPD database was searched using key words "headache", "stomachache" and "dysmenorrhea" respectively in "diagnosis" option. And 113 recipes for headache, 167 recipes for stomachache and 131 recipes for dysmenorrhea were screened.

Data Analysis

Composition rules were analyzed by "prescription analysis" function in the "data analysis" module in Traditional Chinese Medicine Inheritance Support System (TCMISS), using data mining method such as association rules analysis and complex system entropy method integrated in the software. In association rules analysis, formula (as shown below) often applied to describe the drug-drug and drug-disease relationships. In most cases, the higher the support degree is, the closer correlation between drugs as well as drug-disease is. However, sometimes, a definite value can not fully display the whole composition rules between drugs and diseases. Therefore, for each disease three support degrees were chosen to illustrate the drug-drug and drug-disease correlation. The formula is as below:

$$\text{Support (A} \rightarrow \text{B)} = P(\text{A} \cup \text{B}) = \frac{\text{sum (A\&B)}}{\text{sum}} \times 100\%$$

RESULTS

Statistical Reports

A total of 113 recipes for headache involving 319 kinds of drugs, 167 recipes for stomachache involving 319 kinds of drugs, and 131 recipes for dysmenorrhea involving 281 kinds of drugs were extracted from the system. Top 25 drugs frequently used in treating headache, stomachache, and dysmenorrhea were obtained by frequency statistics (Table 1). Syndrome distribution of the used recipes is shown in Table 2.

Association Rules Analysis on Recipes Treating Headache

By using association rules analysis, the support degree was set to 10%, and 51 drug pairs and combinations were obtained (Appendix 1). The associated networks were shown in Figure 1 using different support degree 10%, 12.5% and 15% respectively to show the relationship among drugs dynamically. In the commonly used drug pairs and combinations, the most commonly used are *Chuanxiong Rhizoma* and *Glycyrrhizae Radix Et Rhizoma*; *Chuanxiong Rhizoma* and *Angelicae Dahuricae Radix*; *Chuanxiong Rhizoma* and *Angelicae Sinensis Radix*; *Glycyrrhizae Radix Et Rhizoma* and *Angelicae Dahuricae Radix*; *Notopterygii Rhizoma Et Radix* and *Saposhnikovia Radix*. These combinations are the core part of the famous prescription Chuanxiong Chatiao Powder (川芎茶调散), for dispelling cold and alleviating pain.

Association Rules Analysis on Recipes Treating Stomachache

Using association rules, the support degree was set to 12.5%, and 33 drug pairs and combinations were obtained (Appendix 2). The associated networks are shown in Figure 2 using different support degree 10%, 12.5% and 15% respectively to show the relationship among drugs dynamically. The most commonly used herb pairs and compositions are *Glycyrrhizae Radix Et Rhizoma* and *Paeoniae Radix Alba*, *Glycyrrhizae Radix Et Rhizoma* and *Cyperii Rhizoma*, *Glycyrrhizae Radix Et Rhizoma* and *Citri Reticulatae Pericarpium*, *Aucklandiae Radix* and *Glycyrrhizae Radix Et Rhizoma*, *Glycyrrhizae Radix Et Rhizoma* and *Amomi Fructus*, *Aucklandiae Radix* and *Citri Reticulatae Pericarpium*.

Table 1. Top 25 CHMs of Medication Frequency

No.	Headache		Stomachache		Dysmenorrhea	
	CHM	Freq.	CHM	Freq.	CHM	Freq.
1	<i>Chuanxiong Rhizoma</i> (Chuanxiong)	41	<i>Glycyrrhizae Radix Et Rhizoma</i> (Gancao)	71	<i>Angelicae Sinensis Radix</i> (Danggui)	95
2	<i>Glycyrrhizae Radix Et Rhizoma</i> (Gancao)	36	<i>Aucklandiae Radix</i> (Muxiang)	52	<i>Chuanxiong Rhizoma</i> (Chuanxiong)	72
3	<i>Angelicae Sinensis Radix</i> (Danggui)	31	<i>Corydalis Rhizoma</i> (Yanhusuo)	48	<i>Paeoniae Radix Alba</i> (Baishao)	66
4	<i>Angelicae Dahuricae Radix</i> (Baizhi)	29	<i>Citri Reticulatae Pericarpium</i> (Chenpi)	48	<i>Cyperi Rhizoma</i> (Xiangfu)	60
5	<i>Scutellariae Radix</i> (Huangqin)	18	<i>Paeoniae Radix Alba</i> (Baishao)	46	<i>Glycyrrhizae Radix Et Rhizoma</i> (Gancao)	52
6	<i>Rehmanniae Radix</i> (Dihuang)	18	<i>Cyperi Rhizoma</i> (Xiangfu)	41	<i>Rehmanniae Radix Praeparata</i> (Shudihuang)	49
7	<i>Notopterygii Rhizoma Et Radix</i> (Qianghuo)	18	<i>Amomi Fructus</i> (Sharen)	39	<i>Atractylodis Macrocephalae Rhizoma</i> (Baizhu)	46
8	<i>Saposhnikoviae Radix</i> (Fangfeng)	17	<i>Magnoliae Officinalis Cortex</i> (Houpo)	32	<i>Leonuri Herba</i> (Yimucao)	43
9	<i>Asari Radix Et Rhizoma</i> (Xixin)	15	<i>Atractylodis Macrocephalae Rhizoma</i> (Baizhu)	30	<i>Poria</i> (Fuling)	41
10	<i>Salviae Miltiorrhizae Radix Et Rhizoma</i> (Danshen)	15	<i>Sepiae Endoconcha</i> (Haipiaoxiao)	28	<i>Corydalis Rhizoma</i> (Yanhusuo)	41
11	<i>Borneolum Syntheticum</i> (Bingpian)	15	<i>Amomi Fructus Rotundus</i> (Doukou)	26	<i>Cinnamomi Cortex</i> (Rougui)	36
12	<i>Menthae Haplocalycis Herba</i> (Bohe)	14	<i>Aurantii Fructus</i> (Zhiqiao)	25	<i>Aucklandiae Radix</i> (Muxiang)	35
13	<i>Achyranthis Bidentatae Radix</i> (Niuxi)	14	<i>Cinnamomi Cortex</i> (Rougui)	23	<i>Asini Corii Colla</i> (Ejiao)	30
14	<i>Paeoniae Radix Rubra</i> (Chishao)	13	<i>Aquilariae Lignum Resinatum</i> (Chenxiang)	22	<i>Carthami Flos</i> (Honghua)	29
15	<i>Polygoni Multiflori Radix</i> (Heshouwu)	13	<i>Poria</i> (Fuling)	22	<i>Salviae Miltiorrhizae Radix Et Rhizoma</i> (Danshen)	29
16	<i>Gastrodiae Rhizoma</i> (Tianma)	13	<i>Bletillae Rhizoma</i> (Baiji)	20	<i>Artemisiae Argyi Folium</i> (Aiye)	25
17	<i>Gardeniae Fructus</i> (Zhizi)	11	<i>Crataegi Fructus</i> (Shanzha)	20	<i>Amomi Fructus</i> (Sharen)	24
18	<i>Poria</i> (Fuling)	11	<i>Caryophylli Flos</i> (Dingxiang)	19	<i>Moutan Cortex</i> (Mudanpi)	24
19	<i>Rhei Radix Et Rhizoma</i> (Dahuang)	11	<i>Alpiniae Officinarum Rhizoma</i> (Gaoliangjiang)	18	<i>Codonopsis Radix</i> (Dangshen)	22
20	<i>Carthami Flos</i> (Honghua)	11	<i>Citri Reticulatae Pericarpium Viride</i> (Qingpi)	18	<i>Scutellariae Radix</i> (Huangqin)	21
21	<i>Schizonepetae Herba</i> (Jingjie)	10	<i>Astragalus Radix</i> (Huangqi)	18	<i>Astragalus Radix</i> (Huangqi)	20
22	<i>Uncariae Ramulus Cum Uncis</i> (Gouteng)	10	<i>Salviae Miltiorrhizae Radix Et Rhizoma</i> (Danshen)	16	<i>Citri Reticulatae Pericarpium</i> (Chenpi)	19
23	<i>Coptidis Rhizoma</i> (Huanglian)	10	<i>Rhei Radix Et Rhizoma</i> (Dahuang)	16	<i>Rehmanniae Radix</i> (Dihuang)	18
24	<i>Chrysanthemi Flos</i> (Juhua)	10	<i>Angelicae Sinensis Radix</i> (Danggui)	15	<i>Dipsaci Radix</i> (Xuduan)	18
25	<i>Platycodonis Radix</i> (Jiegeng)	10	<i>Toosendan Fructus</i> (Chuanlianzi)	15	<i>Ginseng Radix Et Rhizoma</i> (Renshen)	17

Notes: CHM: Chinese herbal medicine; Freq: frequency

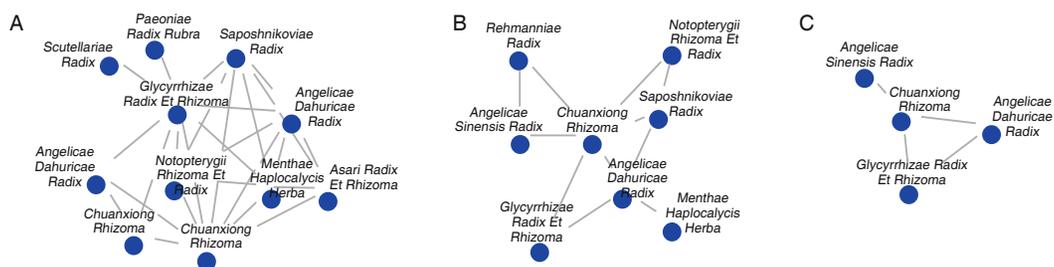


Figure 1. Commonly Used CHM Combinations for Treatment of Headache

Notes: Support degree: A=10%, B=12.5%, C=15%

Table 2. Syndrome Distribution of Recipes in Treating Pain

No.	Headache		Stomachache		Dysmenorrhea	
	Syndrome	Freq.	Syndrome	Freq.	Syndrome	Freq.
1	Ascendant hyperactivity of Gan (Liver) yang	15	Disharmony between Gan and Stomach	27	Qi stagnation and blood stasis	35
2	Wind, cold and dampness congealing in muscle and tendon	11	Qi stagnation in middle energizer	26	Static blood blocking in uterus	34
3	Disquieted Xin (heart) spirit	11	Qi stagnation and blood stasis	15	Mutual deficiency of blood and qi	27
4	Wind attacking head	9	Yang deficiency in both Pi (Spleen) and Wei (Stomach)	14	Uterine vacuity cold	24
5	Qi stagnation and blood stasis	7	Qi stagnation and Gan obstruction	12	Injuries in muscle and tendon	8
6	Gan fire flaming up	7	Wei burn and qi stagnation	11	Blood deficiency	8
7	Wind invading body	7	Qi stagnation in both Pi and Wei	9	Blood deficiency and Gan obstruction	7
8	Exuberant heat toxicity	6	Food retention	9	Wind, cold and dampness congealing in muscle and tendon	6
9	Mutual deficiency Gan and Shen (Kidney)	5	Qi stagnation and blood stasis in Wei	9	Cold congealing in uterus	5
10	External invasion by wind and heat	4	Cold congealing and qi stagnation	7	Disharmony between Gan and Wei	3

Note: Freq: frequency

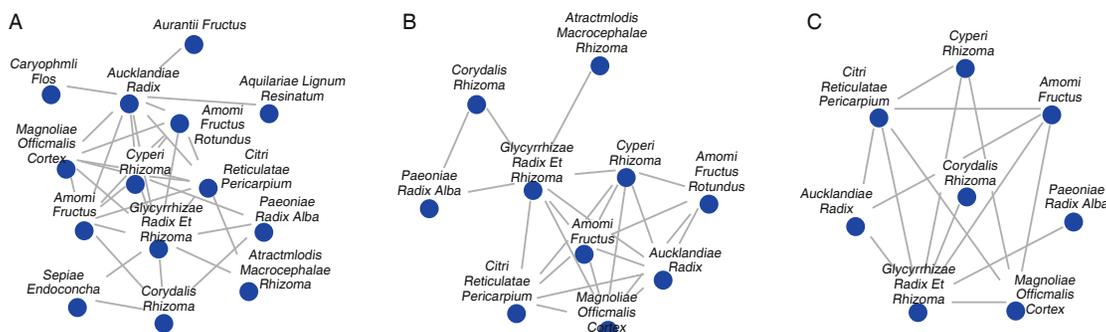


Figure 2. Commonly Used CHM Combinations for Treatment of Stomachache

Notes: Support degree: A=10%, B=12.5%, C=15%

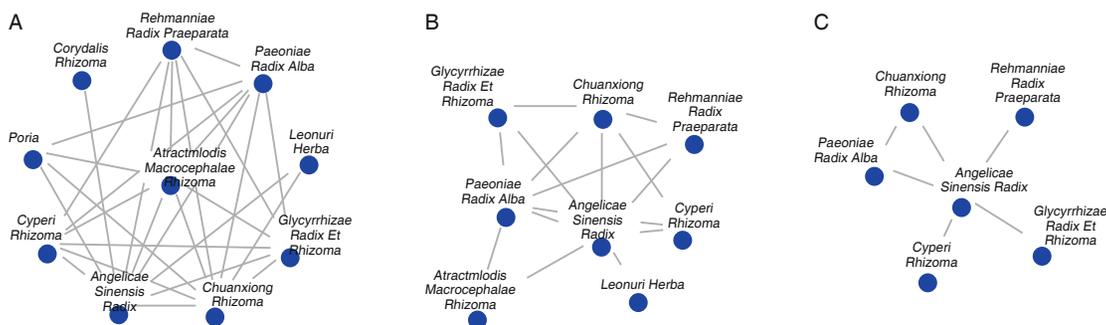


Figure 3. Commonly Used CHM Combinations for Treatment of Dysmenorrhea

Notes: Support degree: A=25%, B=30%, C=35%

Association Rules Analysis on Recipes Treating Dysmenorrhea

Using association rules, the support degree was set to 30%, and 22 drug pairs and combinations were obtained (Appendix 3). The associated network between drugs are shown in Figure 3 using different support degree 25%, 30% and 35%, respectively to

show the relationship among drugs dynamically. The most commonly used herb pairs and compositions are *Chuanxiong Rhizoma* and *Angelicae Sinensis Radix*, *Paeoniae Radix Alba* and *Angelicae Sinensis Radix*, *Angelicae Sinensis Radix* and *Cyperi Rhizoma*, *Chuanxiong Rhizoma* and *Paeoniae Radix Alba*, all of which are the components of the classic formula,

Siwu Decoction (四物汤), the basic formula for treating gynecological patterns.

DISCUSSION

For the pain related diseases, CM treatment is always based on the law "eliminating obstruction and nourishing muscular and vessel". Due to the different sites of pains, the etiologies and pathogenesis of formation are also different, as well as the specific medication. CPM in NSCPD, recording the clinical effective recipes, is a good carrier for the composition rule, and from which we can summary prevention and treatment laws in CM. Headache, stomachache and dysmenorrhea are common pain syndromes, and in most cases, CM considers that these pain syndromes are resulted from the upper invasion of wind, disharmony of Wei (Stomach) qi, stagnation and obstruction in blood aspect respectively. Therefore, although these diseases are treated by "eliminating obstruction and nourishing muscular and vessel" method, there are certain differences when using treating methods of dispelling wind and relieving pain, nourishing Wei and relieving pain, regulating qi and blood as treatment law.

Headache disease locates in the head, and wind, fire, stasis and deficiency are the pathogenic factors. It is caused by the dysfunction of upper orifices obstructions or malnutrition of meridians and collaterals. It should be treated based on the principle of nourishing spirit and clearing upper orifices and method of alleviating pain. CM patent drugs records 113 recipes for headache involving 319 kinds of drugs, and the top commonly used drugs have the treating effect of regulating qi, activating blood, dispelling wind and alleviating pain. Most of them are of mild nature, with the bitter taste and with entry to liver meridian. In the recipes for headache, there are 42 recipes containing *Chuanxiong Rhizoma*, which is the most commonly used drugs, and the common compatible drugs are *Glycyrrhizae Radix Et Rhizoma*, *Angelicae Dahuricae Radix*, *Angelicae Sinensis Radix*; *Angelicae Sinensis Radix*, *Notopterygii Rhizoma Et Radix*, etc. It fully reflects the understanding of "head is most commonly invaded by wind", and indicates that dispelling wind and alleviating pain is the basic principle of headache treatment.

Stomachache is caused by the dysfunction of stomach in digestion and absorption, disharmony of Wei qi and disorder of qi movement, all of which can be given up to by different factors. The disordered

organ of diseases with the symptom of stomachache is stomach and it also relates closely with Pi (Spleen) and Gan (Liver). In this aspect, the general principle of treatment is regulating qi and harmonizing Wei. There are 167 prescriptions with the main therapeutic effect of relieving stomachache being recorded in NSCPD, including 319 metaria medica. The top used herbs have the therapeutic effects of regulating qi, relieving pain, tonifying Pi and harmonizing Wei and possess a mild nature, a pungent taste and with the attribution to spleen meridian. The most commonly used herb pairs have the therapeutic effects of harmonizing stomach and alleviating pain and reflect the treatment principle of diseases with stomachache. *Paeoniae Radix Alba* and *Glycyrrhizae Radix Et Rhizoma* is not only a commonly prescribed herb pair, but a classic formula with the therapeutic effect of emolliating Gan and relieving pain, being used in all kinds of pain syndrome. In the prescription with the indication of stomachache, there are 46 prescriptions containing the herb pair of *Glycyrrhizae Radix Et Rhizoma* and *Paeoniae Radix Alba*. Other commonly used herbs are *Corydalis Rhizoma*, *Cyperi Rhizoma*, *Salviae Miltiorrhizae Radix Et Rhizoma*, *Atractmlodis Macrocephalae Rhizoma*, etc., all of which have the therapeutic functions of regulating qi, relieving pain, tonifying Pi and harmonizing Wei.

The occurrence of dysmenorrhea is closely related to periodical physiological changes in the uterus, vital vessel and conception vessel. The general principle of treatment is tonifying and regulating qi and blood. There are 131 prescriptions being recorded in NSCPD with the main therapeutic effect of treating dysmenorrhea, involving 281 materia medica. The most commonly used herbal medicine have the therapeutic functions of nourishing blood, activating qi and relieving pain. They are of the mild nature, have pungent taste and attribute to Gan meridian. *Angelicae Sinensis Radix* is an essential element in treating gynecological diseases. There are 96 prescriptions containing *Angelicae Sinensis Radix* among the formulae and patent medicine for gynecological diseases. In this aspect, *Angelicae Sinensis Radix* is the most commonly used element always being prescribed together with *Chuanxiong Rhizoma*, *Paeoniae Radix Alba* and *Cyperi Rhizoma*. *Angelicae Sinensis Radix* is used in combination with *Chuanxiong Rhizoma* for mutual reinforcement, which have the therapeutic effects of nourishing and tonifying blood, regulating menstruation and

relieving pain. This herb pair is widely used in clinical treatment in pattern of qi stagnation and blood stasis. There are 69 prescriptions containing herb pair of *Angelicae Sinensis Radix* and *Chuanxiong Rhizoma*, and the commonly used herbs are *Rehmanniae Radix Praeparata*, *Paeoniae Radix Alba*, *Atractylodis Macrocephalae Rhizoma*, *Cyperus Rhizoma* and *Leonuri Herba*, etc., with the therapeutic effects of nourishing blood and activating qi, which further reflects that the classic formula, Siwu Decoction is the basic and core prescription in treating dysmenorrhea.

Finally, to make conclusions: for headache, stomachache and dysmenorrhea, the three pain-related diseases, occurring in different parts, upper, middle and lower part of human body, there exist some similarities in the treatment, but their focuses might be different. To be specific, in the headache and dysmenorrhea treatments, drugs nourishing the blood and promoting blood circulation are commonly used. Besides, for headache treatment removing pathogenic wind is also indispensable, while for dysmenorrhea it is unnecessary. The same thing happened in stomachache and dysmenorrhea as well, the treatment focused on regulating qi to alleviate pain, which varied from headache treatment. Therefore, the article analyzed the composition rules treating three pain-related diseases on assist of data mining methods, which discovered the composition rules of three diseases and similarities and differences between them, which could provide references for the clinical application and new drug design for headache, stomachache and dysmenorrhea.

Conflict of Interest

We declare that we have no financial and personal relationships with other people or organizations that can inappropriately influence our work, and there is no professional or other personal interest of any kind in any product, service and/or company that could be considered as influencing to the paper.

Author Contributions

Yang HJ designed the project, Shen D collected the data, cleaned it and made primary data mining via TCMISS, Tang SH made deep analysis on the data and wrote the paper.

Electronic Supplementary Material: Supplementary material is available in the online version of this article at <http://dx.doi.org/10.1007/s11655-017-2957-z>.

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(Accepted February 22, 2015; First Online August 24, 2017)

Edited by YUAN Lin